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SECONDARY ANEMIA OF INFANTS

A STUDY OF SO-CALLED INFANTILE SPLENIC ANEMIA OR ANEMIA INFANTUM PSEUDOLEUKEMICA

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It is evident from a study of pediatric and hematologic literature that great confusion exists concerning the nature and significance of the various types of anemia occurring in infancy, particularly in regard to that symptom complex spoken of as von Jaksch's anemia. This confusion is due to the attempt to apply the criteria used for adults to the interpretation of the blood picture in infants, and also to the failure to appreciate the peculiarities of the response of the infantile hematopoietic system to infection and anemia. A lymphocytic reaction is frequently observed in infants with anemia and has been confused with leukemia. Enlargement of the spleen, prematurity, faulty feeding, nutritional disorders, rickets, and other conditions, introduce additional factors which complicate the study of blood disorders in infancy. These various factors must not be considered singly, but in relation to each other, if we would appreciate fully the peculiarities of the blood picture observed in infants. This report is based on a study of infants with anemia. The attempt will be made to show that the anemias so frequently encountered in infants with rickets, nutritional disorders, and other conditions associated with enlargement of the spleen, liver or lymph nodes, and with quantitative and qualitative changes in the blood picture (such as, anemia, leucocytosis, erythroblastosis, lymphocytosis, myelocytosis) are merely secondary anemias with varying predominant types of reaction.

Although some studies of infantile anemias had been made by Gretsell[1] in 1866 and by Somma[2] in 1884, it was not until the appearance of papers by von Jaksch[3] in 1899 and 1890 that attention was directed to a peculiar type of anemia often seen in infancy. Von Jaksch described four cases in his two papers which showed, in addition to a diminution in the red blood cells and hemoglobin, some poikilocytosis, a leucocytosis and enlargement of the liver, spleen and lymph nodes. Rickets was present in at least two of these cases. No mention was made of qualitative changes in the blood picture other than increase of eosinophiles. Von Jaksch believed that the condition encountered in these patients was a clinical entity; and that it was to be differentiated from leukemia because the liver was not so large, the anemia was more severe, rickets was usually present, and the malady in itself was not fatal. He suggested the name "anemia infantum pseudoleukemica." At about the same time Di Lorenzo[4] described some cases

showing essentially similar features and expressed the opinion that they were due to an infectious agent. He used the term "anemia splenica infettiva dei bambini." Hayem,[8] in 1889, also presented a case of anemia in an infant and called attention for the first time to the presence of nucleated red blood cells. Luzet[9] in presenting a series of similar cases two years later, emphasized not only the leucocytosis and splenomegaly, but also the presence of nucleated red blood cells. He excluded from this group any patient with rickets or syphilis. The early papers, although not establishing the status of these cases very clearly, served to stimulate interest in them. A number of contributions on the subject followed, and much discussion arose as to whether the cases described were splenic anemia or leukemia, whether they were dependent upon rickets, or were infectious in origin. They were often referred to as von Jaksch-Hayem-Luzet anemia. In general, the following opinions were set forth:

1. Splenic anemia of infants was a secondary anemia (Fischl,[7] Ostrowski,[8] Naegeli,[9] Stengel,[10] Ashby,[11] Wentworth,[12] Flesch,[13] Lichtenstein [14]).

2. It represented an aleukemic stage of true leukemia (Luzet [9]).

3. It represented a transition between pernicious anemia and leukemia (Engel [15]).

4. It stood midway between simple anemia and leukemia (Hutchison [16]).

5. It was a disease *sui generis*, a primary anemia (von Jaksch,[2] Alt and Weiss,[17] Melland,[18] Fowler [19]).

6. It represented a myeloid leukemia of infancy (Lehrndorf [20]).

7. It was a splenomedullary pseudo-leukemia (Pappenheim [21]).

8. It was a primary disorder of the bone-marrow due to rickets (Marfan,[22] Aschenheim and Benjamin [23]).

Although the significance of the findings in these cases was so little understood, the criteria for diagnosis became more numerous and more clearly defined as more cases were described. Gradually there developed a definite clinical picture usually spoken of as "anemia infantum pseudoleukemica" or "splenic anemia of infants." Infants chiefly from six to twenty months of age were affected. Frequently no other disease was demonstrable, rickets was often, though not always, present, and occasionally prematurity and various infections as syphilis, tuberculosis, malaria, leishmaniasis, were found. A waxy or lemon yellow color of the skin was commonly observed. The spleen was always enlarged, but the enlargement might be either slight or of severe grade. The liver was often a little enlarged, but sometimes was of normal size. There was slight general enlargement of the lymph nodes in some cases. Anemia either slight, moderate, or severe was always present with a color index of one or less than one and with poikilocytosis, anisocytosis and polychromasia. The total white blood cell count was sometimes normal, but there was often a leucocytosis, occasionally very severe. A relative lymphocytosis was common; and immature myeloid cells, pathological lymphoid forms, and nucleated red blood cells were frequently found, sometimes in great numbers. The mortality was high, due not to the condition *per se*, but rather to secondary infection. It is interesting that this clinical picture, which is so much broader in its scope than the one originally described by von Jaksch, is still frequently referred to as "von Jaksch's anemia."

All the various manifestations encountered in these cases excited discussion, and attempts were made to determine the relation of each to the entire symptom complex. The frequency of rickets as an associated condition was noted early, and mentioned in nearly every report on the subject. Hutchison,[16] in 1904, observed that the rickets was usually not of severe degree, that the cranial bones were frequently affected and showed bosses in the frontal and parietal regions. Rickets was suggested by some as the etiological factor. Aschenheim and Benjamin [23] collected seventy cases from the literature and they considered the relation of rickets to "anemia infantum pseudoleukemica" the same as that of syphilis to tabo-paresis. They considered the disease a degenerative process of the bone-marrow and coined the term "Rachitische Megalosplenie" to emphasize the associated rickets. Aschenheim,[24] in 1912, studied the blood in rickets and attempted to differentiate rickets with mild anemia from rickets with severe anemia. He found that the severity of the rickets was not parallel with the severity of the anemia. Marfan,[22] also, held that the condition was a disorder of the bone-marrow due to rickets.

The variable number of leucocytes found in different cases and in the same case at different times excited comment. Many authors (Ashby,[11] Wentworth,[12] Aschenheim and Benjamin,[23] Lichtenstein [14] and others) insisted that leucocytosis is not essential to the blood picture, that the white blood cells might be diminished, normal, or increased in number, and that very high counts are exceptional.

A relative and absolute increase in lymphocytes has been mentioned repeatedly (Fischl,[7] Geissler and Japha,[25] Fowler,[19] Weil and Clerc,[26] Rivière,[27] Flesch and Schoszberger,[28] Kleinschmidt,[29] Hunter,[30] Hutchison,[16] Aschenheim and Benjamin,[23] Ashby,[11] Ostrowsky,[8] Stettner,[31] Lichtenstein,[14] Hallez [32]). In the case presented by Geissler and Japha, 97 per cent of the white blood cells were lymphocytes, but unfortunately not enough data are available to rule out the possibility of leukemia in this instance. Hutchison reported a case with 79 per cent lymphocytes, Stettner one with 68 per cent, and Lichtenstein one with 81 per cent. This lymphocytosis was often associated with enlargement of the lymph nodes. Both normal and pathological lymphocytes were present. The significance of the lymphoid reactions occasioned some discussion, but they were attributed by most observers merely to the unusual lymphoid activity in infancy.

The pronounced differences in the degree of enlargement of the spleen in these cases has also been given some attention. The variability and consequent lack of importance of the enlargement of the spleen were emphasized by Fischl,[7] Wentworth,[12] Hutchison,[16] Aschenheim,[24] and others. Carpenter [33] stated, "The anemia may be extreme and yet there be no enlargement of the spleen, and on the other hand quite an

appreciable enlargement of the spleen is frequently associated with a very mild form of anemia."

The frequency of infection so often associated with this symptom complex, and the rôle of infection in the production of severe anemia in infancy has been emphasized by Stettner [21] and others. Particularly in Italy the importance of malaria and leischmaniasis has been pointed out.

In addition to the anemias described above under the terms splenic anemia of infants or anemia infantum pseudoleukemica, others have been described as a separate group; "chlorotic anemia of infants," "alimentary anemia" (Kleinschmidt,[29] Swartz and Rosenthal,[34] Lichtenstein [11]). In these cases the blood picture varied from merely a reduction of hemoglobin to one approaching the type presented above. The anemia was attributed to a deficient supply of iron due to a prolonged milk diet or to underfeeding. Likewise, the frequent occurrence of anemia in premature infants has been noted often, and attributed to a deficient store of iron (Bunge [28]) and to a failure of the hematopoietic system to develop (Lichtenstein [11]). The anemias of these infants presented a blood picture of the simple chlorotic type or one resembling rather closely that referred to as "anemia infantum pseudoleukemica."

In this study only cases have been presented in which syphilis, tuberculosis, all known specific causes for enlargement of the spleen, liver and lymph glands, and all primary diseases of these organs and the bone-marrow, were ruled out, as far as possible, by clinical procedures. Each case was, therefore, an example of so-called "infantile splenic anemia," or "anemia infantum pseudoleukemica." *

CASE 1.—C. R., a white infant, aged nine months, was admitted to The Harriet Lane Home March 18, 1920, because of failure to gain and anemia.

The patient was born prematurely at the seventh month. Breast feeding was attempted but was unsuccessful, and he was artificially fed on Mellin's food and condensed milk up to the time of admission to the hospital. He received in addition cod-liver oil and orange juice.

Examination on admission showed a poorly nourished infant weighing 12 pounds. The skin and mucous membranes were very pale. The head was large in proportion to the body, square, with prominent frontal bosses, between which there was a deep depression. The sutures were closed, but the anterior fontanelle was widely open and slightly depressed. There was slight cranio-tabes. The eyeballs were rotated downwards, exposing the sclera above the cornea. The lungs were clear. There was no enlargement of the epiphyses of the long bones, nor any deformities of the extremities, thorax or spine. The anterior and posterior cervical glands were palpable, but there was no general lymph-glandular enlargement. The spleen was enlarged, filling the entire left flank, the lower edge entending to the anterior superior spine. The edge was firm and smooth. The liver edge was just felt at the right costal margin.

The Pirquet and Wassermann tests were negative. X-rays of the head, chest and extremities showed mild rickets. The blood picture showed moderate reduction in red blood cells, a severe reduction of hemoglobin, slight anisocytosis and poikilocytosis, rather pronounced basophilia and a few nucleated forms; and a leucocytosis with an essentially normal differential formula (see Table I).

During his stay in the hospital the infant developed otitis media and acute bronchitis with elevations of the temperature to 102° F. Treatment consisted in a diet of milk, barley water and sugar mixture, cereals, broth, orange juice, and cod-liver oil (one drachm three times a day). He improved somewhat and reached a weight of 13½ pounds on April 21, 1920, when he was discharged. He has not been seen since that time.

This case, of a premature infant, artificially fed, with mild rickets and severe infections, showed, with a marked enlargement of the spleen and slight enlargement of the liver, merely a simple secondary anemia. The findings in this patient are to be compared with those in Case 2 in which there was slight enlargement of the spleen, and with those in Case 3 in which splenomegaly was not present. In both of these cases the blood picture was essentially the same as in this patient, differing from it only in the degree of anemia present and the percentage of lymphocytes found.

CASE 2.—E. S., a white infant, aged 11 months, was admitted to The Harriet Lane Home May 19, 1920, because of failure to gain weight.

Birth was premature at the seventh month; the birth weight was 2¼ pounds. The patient did not gain properly, although various milk preparations were tried and at times a wet nurse was secured. For two months the patient had had breath-holding spells. There had been no vomiting or diarrhœa.

Examination on admission showed a small, undernourished infant, weighing 8 pounds. The skin and mucous membranes were pale. The head was short anteroposteriorly with high forehead and full fontanelle. Cranio-tabes was present. The epiphyses of the long bones were slightly enlarged and X-rays of these showed rickets. The abdomen was distended. There was no enlargement of the lymph nodes. The spleen was felt one finger's breadth below the costal margin. The liver was not felt.

The Pirquet and Wassermann tests were negative. The blood in this case showed a moderate reduction in red blood cells and hemoglobin, some anisocytosis and poikilocytosis, slight diffuse basophilia; and a slight leucocytosis at one time with a moderate lymphoid reaction (see Table II).

The patient has remained in the hospital since admission. She has gained slowly in weight (at present she weighs 13 pounds). Cereals and meat were added to the milk diet and she was given, in addition, cod-liver oil and reduced iron. There has been slight improvement in her general condition.

This case is that of a premature child, badly fed and with mild rickets, who showed, with a slightly enlarged spleen, a blood picture essentially that of a simple secondary anemia. This case is to be compared with Case 1 having a large spleen, and with Case 3 showing no enlargement of the spleen, both of which presented the same type of blood picture.

CASE 3.—G. E., a colored infant, aged eight months, was admitted to The Harriet Lane Home May 12, 1920, because of fever.

Birth was premature at the seventh month. The patient was breast fed for three months and then weaned to a whole milk mixture supplemented by orange juice, but no other food. For two weeks there

* The abbreviations for white blood cells in the blood charts are as follows:

P. M. N.—polymorphonuclear neutrophile.
P. M. E.—polymorphonuclear eosinophile.
P. M. B.—polymorphonuclear basophile.
S. L.—normal small lymphocyte.
L. L.—normal large lymphocyte.
P. L.—pathological lymphoid forms.
L. M. } —cells of the large mononuclear-transitional cell group—
Trans. } oxydase mononuclears.

The hemoglobin is expressed in percentage, as estimated by the Sahli apparatus.

had been fever and difficulty in breathing. Examination on admission showed a fairly well-nourished infant weighing 12 pounds. The skin and mucous membranes were strikingly pale. There was enlargement of the epiphyses and costochondral junctions, but no deformities. A systolic murmur was heard over the heart, and scattered patchy consolidations of the lungs were made out. There was slight general enlargement of the lymph nodes. The liver and spleen were not felt.

The Pirquet and Wassermann tests were negative. X-rays of the extremities showed rickets. The blood in this case showed a moderately severe reduction in the number of red blood cells, a severe reduction in hemoglobin, moderate anisocytosis and poikilocytosis, slight basophilia, a few nucleated forms, and a moderately severe leucocytosis, showing the presence of practically no immature forms but with a wide variation in the relative percentage of myeloid and lymphoid cells between counts done ten days apart (see Table III).

The patient reacted poorly to the pulmonary infection and died May 24, 1920. *Autopsy findings:* Rickets, confluent pneumonia, fatty changes in heart and liver.

This patient born prematurely and then artificially fed and having severe rickets and an acute infection, with slight general glandular enlargement but no enlargement of the spleen or liver, showed a blood picture essentially that of a simple secondary anemia with leucocytosis. This case is to be compared with Case 1 in which a premature infant with mild rickets showed, in the presence of marked enlargement of the spleen, about the same blood picture. The reaction of the blood is of interest in connection with the question, "Are the blood changes seen in so-called von Jaksch's anemia merely an infantile response to demands for increased hematopoietic activity?" Here there is an anemia and a call for leucocytes, yet the blood picture is not that commonly spoken of as von Jaksch's anemia, but only that of a simple secondary anemia with leucocytosis.

Case 4.—D. B., a white infant, aged nine months, was admitted to The Harriet Lane Home August 23, 1919, because of anemia.

The patient was a premature infant, born at the sixth month and was said to have weighed only two pounds at birth. He was never breast fed. Condensed milk feedings were given for four months, and following this a whole milk mixture with orange juice. He was able to sit up and had gained fairly well in weight, but for several months the mother had noticed a pale yellow color of the skin.

Examination on admission showed a fairly well-nourished white boy, weighing 13½ pounds. The skin and mucous membranes were pale with a lemon yellow tint. There was, however, no jaundice. The head was large with prominent frontal bosses and flattened posteriorly. The anterior fontanelle was almost closed. The thorax was of normal shape. There was a systolic murmur heard over the heart. There was slight epiphyseal enlargement of the long bones but no deformities. The lymph glands were not enlarged. The spleen was felt 2 cm. below the left costal margin, definitely palpable but not much enlarged. The liver was not palpable.

The Pirquet and Wassermann tests were negative. The blood in this case showed a moderately severe reduction in red blood cells and hemoglobin, a minimal amount of anisocytosis and poikilocytosis, a slight grade of diffuse basophilia, with no nucleated forms; and a moderate leucocytosis, at one time a high lymphocyte percentage, and also the presence of a few immature myeloid cells (see Chart IV).

The patient was given a diet consisting of whole milk mixture and cereals. He was taken to another hospital August 26, 1919, and there transfused with 75 c.c. of whole blood. He was readmitted to The Harriet Lane Home November 25, 1919, having developed breath-holding spells. Examination revealed no new features, except that the spleen was not palpable. The anemia persisted on a mixed diet with meat and broth. With the administration of ferrum reductum (gr. II, t. i. d.) he improved and was discharged December 14, 1919. When last examined April 15, 1920, he showed marked improvement.

This case of a premature infant, artificially fed, and having very mild rickets showed, with a slight enlargement of the spleen and no enlargement of the liver, a blood picture resembling very closely that seen in Case 5, an infant born at term in which there was no rickets but a moderate enlargement of both the spleen and liver.

Case 5.—J. M., a white boy, aged two years and ten months, was admitted to The Harriet Lane Home September 9, 1919, because of anemia and fever.

The patient was born at term, and was breast fed for two months. After weaning he was given a cow's milk mixture with the gradual addition of other foods so that prior to admission he was taking a general mixed diet including green vegetables, meat and eggs.

Examination on admission showed a well-nourished boy, well developed and active. There was marked pallor of the skin and mucous membranes. The head was somewhat large in proportion to the body and the frontal bosses were prominent. There were no other evidences of rickets. A systolic murmur was heard over the precordium. The cervical, axillary and inguinal lymph glands were moderately enlarged. The spleen edge was felt three fingers' breadth below the left costal margin. There was a bilateral otitis media and myringotomy was performed. Examination of the naso-pharynx showed a mass of adenoid tissue.

The Pirquet and Wassermann tests were negative. The temperature was slightly elevated (100° F.), due to the otitis media. The blood showed a slight diminution of the red blood cells, a more severe diminution in hemoglobin, a minimal amount of anisocytosis and poikilocytosis, practically no basophilia, no nucleated forms; and a slight leucocytosis showing a moderate lymphoid reaction with, at times, the presence of many immature forms, and an occasional immature myeloid cell (see Table V).

Treatment consisted in care of the otitis media, a mixed diet and ferrum reductum (gr. II, t. i. d.). The patient improved and gained in weight; the spleen diminished in size so that, on discharge from the hospital October 2, 1919, the edge was only palpable. The size of the liver remained unchanged.

This case is an example of a full-term child, properly fed, without rickets but having a mild infection, who showed, with a moderate general glandular enlargement and moderate enlargement of the spleen and liver, a mild secondary anemia with leucocytosis, a high percentage of lymphocytes, and a few immature lymphoid and myeloid cells.

Case 6.—J. S., a white infant, aged 20 months, was admitted to The Harriet Lane Home June 8, 1919, because of refusal to take food.

The patient was born prematurely at the ninth lunar month and weighed five pounds at birth. He was artificially fed from birth and difficulty had always been experienced in getting him to take food. He had not received any addition to a milk mixture diet on this account. Mental development had been retarded, he had made no attempt to sit or stand and he did not seem to notice objects put before him. When seen in the out-patient department at the age of 13 months, he showed slight enlargement of the spleen, and pallor of the skin and mucous membranes. No blood examinations were made at this time. June 7, 1919, the child had a convulsion which was followed by vomiting and fever. He was admitted to the hospital on the following day.

Examination at that time showed a fairly well-nourished but underdeveloped white infant weighing 13 pounds. There was striking pallor of the skin and mucous membranes. There were no hemorrhages into the skin or mucous membranes. The child paid no attention to

TABLE I.—BLOOD CHART OF CASE 1

Date	R. B. C.	Hb. %	Aniso.	Poikilo.	Basophilia	Normobl.	Megalobl.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. L.	L. L.	P. L.	L. M.	Trans.	Myelocytes	Myeloblasts	Unclass.	Platelets	Remarks
3-18-20	3,520,000	32	+	+	0	2	0	13,600	52.0	.5	1	23.5	3.0	1.0	6.0	3.0	0	0	10.0	Normal.	.....
3-22-20	3,140,000	33	..	..	..	...	...	12,600	....	....	...	....	...	...	...	...	...	...	....	.....	.....
3-26-20	3,740,000	35	+	+	+++	5	1	17,000	51.5	.5	0	23	2.0	2.0	4.0	4.0	0	0	13.0	Normal.	Otitis and bronchitis. Temperature 99 to 103° F.

TABLE II.—BLOOD CHART OF CASE 2

Date	R. B. C.	Hb. %	Aniso.	Poikilo.	Basophilia	Normobl.	Megalobl.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. L.	L. L.	P. L.	L. M.	Trans.	Myelocytes	Myeloblasts	Unclass.	Platelets	Remarks
9- 1-20	3,840,000	65	+++	+	+++	0	0	8,200	36.0	0	0	49.0	.5	1.0	4.5	2.5	.5	0	6.0	Moderately increased.	.....
4-22-21	5,280,000	52	+	+	0	0	0	13,200	48.5	0	.5	20.5	14.0	3.5	3.5	1.0	0	0	8.5	Increased.	.....

TABLE III.—BLOOD CHART OF CASE 3

Date	R. B. C.	Hb. %	Aniso.	Poikilo.	Basophilia	Normobl.	Megalobl.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. L.	L. L.	P. L.	L. M.	Trans.	Myelocytes	Myeloblasts	Unclass.	Platelets	Remarks
5-12-20	2,363,000	27	+	+	+	1	1	17,800	36.0	0	0	42.0	3.0	.5	5.5	6.0	0	0	7.0	Normal.	Bronchopneumonia. Temperature 102° F.
5-23-20	.....	..	+++	+++	+	2	1	18,400	60.0	0	0	16.0	2.4	.4	6.8	4.8	0	0	9.6	High normal.	Temperature 103° F.

TABLE IV.—BLOOD CHART OF CASE 4

Date	R. B. C.	Hb. %	Aniso.	Poikilo.	Basophilia	Normobl.	Megalobl.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. L.	L. L.	P. L.	L. M.	Trans.	Myelocytes	Myeloblasts	Unclass.	Platelets	Remarks
8-23-19	3,500,000	30	+	+	0	0	0	11,000	37.0	5.0	0	43.0	0	5.0	2.0	7.0	1.0	0	0	Diminished.	.....
12- 2-19	2,960,000	40	+	+	+	0	0	12,800	63.6	.8	0	25.6	1.6	4.0	1.2	.8	.4	...	2.0	Normal.	.....
2-28-20	.....	60	+	+	+	0	0	18,000	55.2	2.0	0	14.8	14.4	.4	5.2	2.0	0	0	6.0	Increased.	.....
4-15-20	4,472,000	60	..	..	.....	...	...	12,880	....	.....	....	....	...	...	...	...	...	...	...	.....	.....

TABLE V.—BLOOD CHART OF CASE 5

Date	R. B. C.	Hb. %	Aniso.	Poikilo.	Basophilia	Normobl.	Megalobl.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. L.	L. L.	P. L.	L. M.	Trans.	Myelocytes	Myeloblasts	Unclass.	Platelets	Remarks
9- 7-19	4,200,000	42	+	+	+	0	0	12,200	39.0	2.0	0	54.0	...	2.0	0	1.0	0	0	2.0	Normal.	Temperature 100° F.
9-12-19	4,200,000	46	+	++	0	0	0	12,400	47.0	0	0	18.0	0	22.0	1.0	2.0	0	2.0	8.0	Diminished.	.....
9-19-19	4,300,000	54	+	+	0	0	0	11,200	43.0	5.0	1.0	35.0	...	12.0	0	0	0	0	6.0	Markedly diminished.	.....
9-27-19	4,460,000	72	...	...	.....	.....		8,200	....	...	...	....	...	....	.....	.....	.....	.....	...	.....	.....

his surroundings and did not seem to see; the eyes would not follow a bright light. He was unable to sit up or to support his head. The head was flattened posteriorly with very high forehead and prominent bosses. The fontanelles were closed. There was slight enlargement of the costochondral junctions and slight epiphyseal enlargement. There were, however, no deformities. Ophthalmological examination showed pallor of both discs, but whether this was due to primary optic atrophy or was a result of the severe anemia was not determined. The temperature on admission was 104° F. and remained elevated for 72 hours. There was no evidence of any infection to explain the fever. There was no enlargement of the lymph glands. The spleen edge was felt three fingers' breadth below the left costal margin. The liver edge extended two fingers' breadth below the right costal margin.

The spinal fluid was normal. The Pirquet and intracutaneous tuberculin (0.1 mg. O. T.) were negative. The Wassermann test was negative with blood and spinal fluid, and the mother's Wassermann test was negative. The blood showed a severe secondary anemia with leucopenia and marked relative lymphocytosis (see Table VI).

It was found extremely difficult to feed the patient. He would swallow milk when placed in his mouth, but would not swallow solid food. June 10, 1919, he was transfused with 200 c. c. of citrated whole blood from the mother. There was no marked reaction. Following transfusion the temperature fell to normal and remained so. The general condition of the patient improved and he was taught to swallow solid food and gradually made to take a mixed diet. The spleen decreased in size. The child failed entirely, however, to develop mentally. He was discharged from the hospital July 31, 1919, and reported regularly for examination. No new features developed except occasional convulsions. His spleen has remained palpable and the blindness has persisted. When last seen, July 21, 1921, the patient was well nourished and taking his diet well, but without improvement in his mental development.

The blood picture in this case is extremely interesting and for that reason will be presented in some detail. The red blood cell count, moderately reduced at first, improved under treatment and, although there were some retrogressions, finally became normal and has remained so for two years. The same may be said of the hemoglobin percentage, although the initial reduction was much more severe than that of the red blood cell count. While the anemia was most pronounced, there was a minimal grade of anisocytosis and poikilocytosis and, very rarely, slight diffuse basophilia. The variations in the white blood cell count and differential picture were extremely interesting. During the stage of most severe anemia there was a moderate leucopenia. As the anemia improved the count became normal and later, in the presence of a minor infection, there was a moderate leucocytosis. During the early stages of study at the time the anemia was severe and slight leucopenia was present, there was a most marked reduction in the percentage of myeloid cells amounting on one day to a complete absence. At this same time the lymphocytes were proportionally increased so that on the day when no myeloid cells were present 94 per cent lymphocytes were counted. Among the lymphocytes there was a good percentage of immature pathological forms presenting widely different morphological features. As the anemia improved, the percentage of lymphocytes rapidly became less, giving way to myeloid cells. When the myeloid cells began to return to the capillary circulation, they were largely immature forms so that on one day there were 19 per cent myelocytes and two per cent myeloblasts counted. These rapidly gave way to normal polymorphonuclear cells, however, and at no time again were immature myeloid cells encountered. The immature lymphoid cells were present constantly, at least in small numbers, for many months. The number of platelets present was essentially normal throughout the course of the illness.

This patient, born prematurely, and artificially fed, mentally retarded, with mild rickets and a moderate enlargement of the liver and spleen, had an anemia associated with such a severe lymphoid reaction that it was difficult, if not impossible, to differentiate it from lymphoid leukemia when first seen. Such reactions have been reported, but they are rare; and it should be emphasized that they occur.

Case 7.—M. van W., a white girl, aged three and one-half years, was admitted to The Harriet Lane Home August 1, 1919, for observation.

The patient was born at term and was breast fed for eight months. Following this she was given whole cow's milk and cereals and then a general mixed diet. She had never learned to walk. There was a vague history of convulsions. She had received cod-liver oil and bitter wine of iron for five months prior to admission.

Examination on admission to the hospital showed a poorly-nourished child with marked rickets. The weight was 22 pounds. The head was square, the frontal and parietal bosses prominent. The epiphyses were enlarged and there were marked deformities. There was pronounced pallor of the skin and mucous membranes. The abdomen was prominent, the muscle tone was poor, and the muscles flabby and weak. There was no enlargement of the lymph nodes. The spleen was greatly enlarged reaching the crest of the ilium. The liver was not palpable.

The urine was of low specific gravity, large in amount, with albumin but no casts. It was sterile on culture. The phenolsulphonephthalein excretion was 4 per cent for two hours. Cystoscopic examination revealed a stricture of the right ureter. The fundi oculorum were normal. The blood pressure was normal. The Pirquet and Wassermann tests were negative. X-rays of the head and long bones showed marked rickets. The blood in this case showed a moderately severe reduction in red blood cells and hemoglobin, a moderate grade of anisocytosis, poikilocytosis and basophilia, the presence of a few nucleated forms; and a white blood cell count varying from 7800 to 17,500, showing at all times a lymphoid reaction and a few immature myeloid and lymphoid cells (see Table VII).

The patient did poorly during her stay in the hospital and on August 16, 1919, was transfused without reaction with 175 c. c. of citrated whole blood. Following this the patient improved somewhat, but only temporarily. She refused food, became weaker and died October 28, 1919.

Autopsy findings.—Advanced rickets, anemia, splenomegaly; fatty liver; congenital malformation of the kidneys.

This case is that of a child three and one-half years old, born at term and properly fed who showed a marked enlargement of the spleen and an anemia with a lymphoid reaction and many immature cells of all types. A leucocytosis, although present at times, was not constant. The changes due to rickets in this child were very marked.

Case 8.—E. D., a colored infant, aged six and one-half months, was admitted to The Harriet Lane Home March 17, 1917, because of weakness, failure to develop and jaundice.

The patient was born at term, weighed seven pounds at birth, and had been entirely breast fed. The mother noted on March 3, 1917, that the skin was becoming yellow and that the napkins were stained yellow.

Examination on admission showed a well-nourished, fairly active infant weighing 13 pounds. There was marked jaundice of the skin, sclerae and mucous membranes. The head was symmetrical and had prominent frontal bosses. The anterior fontanelle was widely open. The mucous membranes were pale. A blowing systolic murmur was heard over the heart. There was no enlargement of the epiphyses nor deformities of the thorax, spine or extremities. There was no general enlargement of the lymph glands. The spleen extended two fingers' breadth below the right costal margin.

The Pirquet and Wassermann tests were negative. The blood picture showed a very severe reduction in red blood cells and hemoglobin, pronounced anisocytosis, poikilocytosis and basophilia,

TABLE VI.—BLOOD CHART OF CASE 6

Date	R. B. C.	Hb. %	Aniso.	Poikilo.	Basophilia	Normobl.	Megalobl.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. L.	L. L.	P. L.	L. M.	Trans.	Myelocytes	Myeloblasts	Unclass.	Platelets	Remarks
6- 8-19	2,400,000	20	+	0	0	0	0	7,600	5.0	0	0	60.0	0	17.0	17.0	...	0	0	1.0	Normal.	Fever. (Temp. 104° F.)
6- 9-19	.....	...	0	0	0	0	0	6,800	0	0	0	67.0	0	27.0	4.0	...	0	0	2.0	Normal.	.....
6-10-19	.....	...	+	+	0	0	0	5,400	7.0	0	0	50.0	0	22.0	13.0	...	4.0	0	4.0	Normal.	Transfusion with 200 c. c. citrated blood.
6-11-19	2,900,000	38	+	+	0	0	0	6,400	8.0	0	0	53.0	0	12.0	4.0	...	19.0	2.0	2.0	Slightly diminished.	.....
6-12-19	3,700,000	45	+	+	0	0	0	8,800	30.0	0	0	35.0	0	8.0	15.0	...	1.0	0	11.0	Diminished.	Temperature normal.
6-13-19	3,500,000	50	+	+	0	0	0	7,000	40.0	0	1.0	37.0	0	3.0	13.0	...	0	0	6.0	Increased.	.....
6-14-19	4,600,000	55	+	+	0	0	0	12,500	38.0	0	0	46.0	0	11.0	3.0	...	0	0	2.0	Diminished.	.....
6-17-19	3,800,000	50	+	+	0	0	0	14,500	41.0	0	0	54.0	0	2.0	3.0	...	0	0	0	Normal.	.....
6-20-19	4,496,000	...	..	..	..	..	..	12,700	.....	...	...	.....	....	....	....	...	.....	...	....	.....	.....
6-25-19	4,976,000	66	+	+	+	0	0	9,400	59.0	1.0	0	31.0	0	6.0	1	2	0	0	0	Increased.	.....
7- 6-19	2,944,000	52	+	+	0	0	0	7,240	47.0	2.0	0	36.0	0	7.0	1	6.0	0	0	1	Moderately increased.	.....
7-15-19	4,680,000	75	+	+	0	0	0	6,480	43.0	2.0	0	47.0	0	2.0	0	5.0	0	0	2	Diminished.	Reduced iron begun.
7-22-19	.....	...	+	+	0	0	0	.....	51.0	0	0	33.0	0	2.0	1	7.0	0	0	6	Normal.	.....
7-31-19	5,240,000	76	+	+	0	0	0	13,200	55.0	3.0	0	29.0	0	1.0	2	2.0	0	0	8	Diminished.	.....
8-15-19	5,212,000	74	+	+	0	0	0	12,000	46.0	1.0	0	35.0	0	11.0	2.0	2.0	0	0	3.0	Normal.	.....
9- 2-19	5,784,000	76	0	0	0	0	0	14,400	50.0	2.0	0	23.0	0	12.0	2.0	3.0	0	0	8.0	Diminished.	.....
10- 6-19	.....	...	0	0	0	0	0	13,400	45.0	.5	0	27.5	14.0	1.5	4.5	2.5	0	0	4.5	Diminished.	.....
11-25-19	5,920,000	84	+	+	0	0	0	11,200	46.0	.5	0	26.5	12.0	3.5	1.5	5.5	0	0	4.5	Normal.	.....
12-18-19	4,850,000	82	..	..	..	..	..	17,500	.....	...	...	.....	....	....	....	...	.....	...	....	.....	.....
2-12-20	.....	85	0	0	0	0	0	18,000	42.0	1.5	0	34.0	8.5	3.5	3.0	6.0	0	0	1.5	Increased.	.....
3-29-20	.....	72	0	0	+	0	0	9,500	38.5	.5	0	47.5	3.0	2.5	3.0	2.5	0	0	2.5	Normal.	.....
4-19-20	.....	...	..	..	..	..	..	17,600	.....	...	...	.....	....	....	....	...	....	...	....	.....	.....
4-20-20	4,352,000	76	+	+	0	0	0	12,600	.....	...	...	.....	....	....	....	...	.....	...	....	Normal.	.....
5- 5-20	.....	...	0	0	0	0	0	.....	.....	...	...	.....	....	....	....	...	.....	...	....	High normal.	.....
7-21-20	.....	70	+	+	0	0	0	15,000	40.0	1.5	0	39.5	3.0	0.5	.5	2.5	0	0	7.5	Normal.	.....

TABLE VII.—BLOOD CHART OF CASE 7

Date	R. B. C.	Hb. %	Aniso.	Poikilo.	Basophilia	Normobl.	Megalobl.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. L.	L. L.	P. L.	L. M.	Trans.	Myelocytes	Myeloblasts	Unclass.	Platelets	Remarks
8- 1- 9	2,460,000	43	+	++	+++	3	1	13,350	35.0	6.0	0	33.0	9	9.0	3.0	6.0	1.0	2.0	5.0	Normal.	.....
8-13-19	2,592,000	41	++	++	0	3	0	17,500	70.0	2.0	0	18.0	0	4.0	0	2.0	1.0	0	3.0	Slightly diminished.	8-16-19. Transfusion 175 c.c. citrated whole blood.
8-20-19	3,560,000	60	0	0	0	0	0	9,000	26.0	4.0	5.0	37.0	0	8.0	1.0	5.0	0	1.0	13.0	Diminished	.....
9- 1-19	2,960,000	70	+++	+	+	0	1	14,000	31.0	1.0	0	36.0	0	5.0	5.0	6.0	0	0	16.0	Diminished.	.....
9-26-19	2,496,000	28	.....	....	.....	.....	.....	13,900	.....	.....	.....	....	....	....	....	....	....	....	....	.....	.....
10-10-19	2,336,000	36	.....	...	.....	.....	.....	7,800	.....	.....	.....	....	....	....	....	....	....	....	....	.....	.....
10-17-19	.....	38	0	+	+	0	2	9,300	58.8	2.4	0	17.6	.4	.8	6.4	4.8	1.6	0	7.2	Normal.	.....

and very many nucleated forms; and a normal white cell count showing the presence of immature myeloid and lymphoid cells. The fragility of the patient's red blood corpuscles to hypotonic salt solutions was within the normal limits and identical with those of a normal individual.

The patient was placed on a mixture of cow's milk, barley water and sugar, with the substitution of breast milk when available, and cereals. He was transfused nine times with citrated whole blood in amounts varying from 50 to 115 c.c., a total of 810 c.c., between March 27, and July 16, 1917. Improvement was rapid; the jaundice disappeared and the spleen diminished in size. By August 23, 1917, the patient was taking a mixed diet and had gained a pound and a half in weight. He has remained well since that time.

This case is that of an infant born at term and breast fed who had very mild rickets and some jaundice, and showed, with a moderate enlargement of the spleen and liver, an anemia with many immature cells of all types. There was no leucocytosis.

Case 9.—C. S., a colored infant, aged 14 months, was admitted to The Harriet Lane Home February 4, 1921, because of anemia.

Birth was at term. The patient was breast fed for one month and then given condensed milk, malted milk and whole milk formulæ. At the time of admission he was taking a mixture consisting of 3 parts milk and 1 part water, with cereal twice a day. The patient had begun to stand with support but could not walk.

Examination on admission showed a fairly well-nourished colored infant weighing 15 pounds. The head was asymmetrical with a projection of the left frontal region and a corresponding depression on the right side. There was slight enlargement of the epiphyses but no deformities. The mucous membranes were pale. The abdomen was distended. There was slight but definite general enlargement of the lymph nodes. The spleen was felt three fingers' breadth below the left costal margin and the liver extended three fingers' breadth below the right costal margin.

X-rays of the long bones showed rickets. The Pirquet and Wassermann tests were negative. The temperature was normal. The blood in this case showed a moderately severe reduction in the red blood cells, a very pronounced diminution in hemoglobin, marked anisocytosis, poikilocytosis, and basophilia, and very many nucleated forms; a leucocytosis, sometimes very high, a severe lymphoid reaction, and the presence at most times of immature lymphoid and myeloid elements (see Table IX).

The patient was given a diet of whole milk, cereals, and meat, with the addition of broth, green vegetables, etc., cod-liver oil, and reduced iron (gr. II, t. i. d.). Progress was slow; the patient developed numerous infections (otitis media, rhinitis, varicella, nasal diphtheria, impetigo). On April 13 he was transfused, without reaction, with 100 c.c. citrated whole blood, and on April 29, with 100 c.c. citrated whole blood. The patient improved somewhat and was discharged May 20, 1921.

This case is an example of an infant born at term, properly fed, and having rickets, who showed, with slight general enlargement of the lymph nodes and a moderate enlargement of the spleen and liver, an anemia with leucocytosis, lymphoid reaction and immature cells. It may be compared with Case 8 and Case 10, in which no increase in the total white blood cell count was observed; and with Case 7 in which at different times a leucopenia and a leucocytosis, respectively, were present.

Case 10.—E. B., a colored infant, aged 20 months, was brought to The Harriet Lane Home May 3, 1921, because of a "lump in the side."

The patient was born at the 8th month and was one of twins. Breast feeding was employed until the 8th month, since which time the patient has received a mixed diet of milk, vegetables, cereal, eggs and orange juice. The mother had noted the lump in the left side for three weeks, and she said the child had seemed weak.

Examination on admission showed a small, under-nourished infant weighing 12¼ pounds. The head was of normal shape and size. The conjunctivæ and mucous membranes were pale and on the surface of the hard palate there were a number of hemorrhages. The thorax showed rachitic deformity. The epiphyses of the long bones were somewhat enlarged. The cervical, axillary, inguinal and epitrochlear lymph nodes were enlarged. The abdomen was distended, due chiefly to the large spleen which filled the entire left flank. The liver was slightly larger than normal.

The Pirquet and Wassermann tests were negative. The blood showed a moderate reduction in the number of red blood cells, a more pronounced diminution in hemoglobin, some poikilocytosis and anisocytosis, a most marked degree of diffuse basophilia, and relatively many nucleated red blood cells; a mild lymphoid reaction and many immature myeloid and lymphoid cells with a normal total white blood cell count (see Table X).

The patient was given a mixed diet, cod-liver oil and reduced iron. On May 14, 125 c.c. of citrated whole blood was given with a moderately severe reaction. The patient up to the present time has shown but slight improvement.

This patient, a premature infant with rickets, showed in the presence of slight enlargement of the lymph glands, marked enlargement of the spleen, and slight enlargement of the liver, an anemia presenting a mild lymphoid reaction, many immature cells and no leucocytosis. A similar picture was seen in Case 8, an infant born at term.

When these cases of anemia in infants were examined in detail, it was seen that, although some of the features presented were common to all the patients, others varied within wide limits. Diminution in the number of red blood cells and in the hemoglobin percentage, anisocytosis, poikilocytosis and basophilia were present in all, and in general the severity of these changes varied with the severity of the anemia. All of the patients also showed at least a slight relative increase in cells of the large mononuclear-transitional cell group. Variations in the number and character of the platelets present from time to time were essentially the same in all cases. However, the degree of anemia, the total white blood cell count, the differential white blood cell formula, the presence of immature cells, enlargement of the spleen, liver and lymph nodes, the presence of rickets, the signs of prematurity, and the kind of feeding employed varied within wide limits. An analysis of these findings and their relation to each other permits definite conclusions.

The blood pictures in these cases showed three major types of reaction, or various combinations of them. Pure examples of them were not commonly encountered, and the cases presented here may not be classified according to this grouping. One typical example of each reaction has been presented, however, and the other cases have been chosen to illustrate different degrees and various combinations of them. The three main types of reaction, which were added to those features already presented as more or less common to all cases, were:

Type I.—The blood changes resembled somewhat those seen in simple secondary anemia of adults; that is, there were no

TABLE VIII.—BLOOD CHART OF CASE 8

Date	R. B. C.	Hb. %	Aniso.	Poikilo.	Basophilia	Normobl.	Megalobl.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. L.	L. L.	P. L.	L. M.	Trans.	Myelocytes	Myeloblasts	Unclass.	Platelets	Remarks
3-23-17	1,000,000	20	+++	+++	+++	Numerous.	Numerous.	8,160	48.0	0	0.5	37.5	0	2.0	8.0	0	4.0	0	0	Normal.	.....
4- 6-17	1,800,000	31	.....	.....	.....	.....	.....	6,650	50	0	0	37.5	...	3.5	3	3	2.5	...	0	.....	.....
7-18-17	3,000,000	50	.....	.....	.....	.....	.....	7,000	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	After nine transfusions.

TABLE IX.—BLOOD CHART OF CASE 9

Date	R. B. C.	Hb. %	Aniso.	Poikilo.	Basophilia	Normobl.	Megalobl.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. L.	L. L.	P. L.	L. M.	Trans.	Myelocytes	Myeloblasts	Unclass.	Platelets	Remarks
2- 4-21	2,992,000	20	.....	.....	.....	.....	...	76,000	....	.....	.....	....	....	....	.....	...	.....	...	....	.....	.....
2- 6-21	.....	....	++++	++	++	37	8	54,000	31.6	.4	0	23.2	0	36.0	6.4	...	0	0	2.4	Normal.	.....
2- 8-21	2,560,000	20	+++	+++	++++	Very numerous.	...	32,000	25.0	1.0	1.0	26.0	0	33.0	8.0	...	0	0	3.0	Mod. diminished.	.....
2-12-21	3,168,000	21	++++	+++	0	0	7	16,400	10.8	.4	0	4.4	0	8.8	3.6	...	.4	0	71.6	Normal.	.....
2-18-21	3,552,000	35	+++	+++	++++	0	0	12,000	65.5	2.5	0	10.0	4.0	6.5	6.0	...	1.0	0	4.5	High normal.	.....
2-24-21	3,424,000	36	+++	++++	0	Few.	0	12,800	17.0	5.0	1.0	33.0	5.0	6.0	5.0	...	3.0	0	25.0	High normal.	.....
3-16-21	.....	....	+++	+++	++++	0	1	25,920	50.4	1.6	.4	15.6	3.6	13.6	4.8	...	0	0	10.0	Normal.	.....
3-31-21	3,784,000	46	+++	++	++++	20	0	22,400	20.4	.8	0	36.4	12.4	2.8	20.0	...	1.2	0	6.0	High normal.	.....
4-13-21	3,648,000	48	++++	Sickle cells. ++++	++++	7	1	25,400	50.0	.8	.4	8.4	19.2	2.8	2.4	2.0	0	0	14.0	Normal.	.....
4-14-21	4,048,000	60	++++	++++	+++	11	0	24,200	48.0	.4	.4	27.6	10.0	1.6	5.6	1.6	1.6	0	4.8	Low normal.	Transfusion 100 c. c. citrated blood 4-3-19.
4-21-21	3,448,000	46	+++	+++	+++	Very rare.	0	19,480	47.5	1.0	0	26.0	6.0	0	6.0	5.5	0	0	8.0	High normal.	.....
4-30-21	3,624,000	52	+++	+++	+++	3	0	28,240	40.0	2.0	.5	42.0	2.0	1.5	4.5	4.5	0	0	3.0	Normal.	.....
5-11-21	4,248,000	50	+++	+++	++	0	0	21,000	55.0	1.0	.5	33.5	2.5	2.0	2.5	2.5	0	0	.5	High normal.	Blood taken just before transfusion of 100 c. c. citrated blood.
5-14-21	3,536,000	50	++	++	+	0	0	15,720	39.0	.5	0	44.5	.5	0	9.5	3.5	0	0	2.5	High normal.	Blood taken just before transfusion of 100 c. c. citrated blood.
5-17-21	3,968,000	60	++	++	++	0	0	15,920	45.0	2.5	0	36.5	2.5	0.5	6.0	3.0	0	0	4.0	High normal.	.....

TABLE X.—BLOOD CHART OF CASE 10

Date	R. B. C.	Hb. %	Aniso.	Poikilo.	Basophilia	Normobl.	Megalobl.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. L.	L. L.	P. L.	L. M.	Trans.	Myelocytes	Myeloblasts	Unclass.	Platelets	Remarks
5- 6-21	4,064,000	50	++	+	++++	9	8	10,860	44.0	4.5	.5	23.0	1.5	2.5	11.0	8.0	3.0	0	2.0	Low normal	.....
5-14-21	3,904,000	40	++	++	++++	11	4	10,240	35.6	.0	.8	28.4	6.0	4.4	9.2	6.8	6.0	0	2.8	Low normal	.....
5-18-21	4,072,000	50	+	+	+++	1	0	10,200	50.5	1.5	.0	13.5	2.0	2.5	9.5	8.5	7.5	0	4.5	Low normal	.....
6- 9-19	3,408,000	40	+	+	+++	14	3	15,200	39.0	1.5	.0	32.5	5.5	4.5	3.0	6.5	4.5	0	3.0	Low normal	.....

immature forms and no increase of lymphocytes. Case 1 was a typical example of this reaction. Cases 2 and 3 showed essentially the same blood pictures, but had some increase in lymphocytes and therefore stood midway between Case 1 and the second type of reaction.

Type II.—The blood showed, in addition to the changes of Type I, an increase in the relative proportion of lymphocytes. Case 6 was an example of this type of reaction. Cases 4 and 5 also showed an increase in lymphocytes as the outstanding feature, but had in addition a few immature cells. They, therefore, stood midway between Case 6 and the third type of reaction.

Type III.—The blood showed, as the most pronounced change, immature cells of all types. There was also in these cases some increase in the percentage of lymphocytes. Cases 7, 8, 9 and 10 might be assigned to this group. When there was a leucocytosis, as in Cases 7 and 9, the picture presented was that commonly spoken of as von Jaksch's anemia.

It would seem, therefore, that the simple anemias of infants differed in blood picture from those of adults chiefly by reason of two special reactions, lymphocytic increase and the presence of immature cells. Either one of these might be present alone and in different degrees, or both be found, the relative importance of one toward the other also the subject of wide variation.

In Table XI the salient clinical features and a summary of the blood picture in each case are presented. Study of this chart reveals several points worthy of note.

The age of the patient apparently bore no relationship to the blood picture encountered, or to any of the chief clinical features of the case.

Prematurity was present in six of the cases studied. In these cases no constant quantitative or qualitative blood changes were found. Also different degrees of splenic enlargement were present. It may be said, therefore, even from this small series of cases, that although secondary anemia is frequently observed in infants born prematurely, the changes in the blood are not characteristic, and the degree of splenic enlargement is not constant.

The feeding of these infants was entirely from the breast in one case and either by combination of breast and artificial feeding or by artificial feeding alone in the others. There was no relationship between any particular type of feeding and the character of the anemia or other clinical features present, although the data on this point are perhaps too meagre to permit definite conclusions. Rickets was present in all but one patient in this series, and this child was nearly three years of age. The striking feature of the rickets found in these patients was that, although slight enlargement of the epiphyses and costochondral junctions was present in the majority, pronounced rachitic changes in the cranial bones were evident. No relationship between the degree of rickets and the severity of the anemia or the type of blood reaction could be demonstrated. Similarly, the severity of the rickets did not parallel the degree of enlargement of the spleen, liver, or lymph nodes.

TABLE XI

Case	Age	Prematurity	Feeding	Rickets	Enlargement of lymph glands	Enlargement of spleen	Enlargement of liver	Infection	Other conditions	Blood
1	9 mos.	7th mo.	Art.	Mild	0	Marked	Slight	Otitis media bronchitis	.....	Moderately severe, simple secondary anemia and leucocytosis.
2	11 mos.	7th mo.	Br. and art.	Mild	0	Slight	0	0	.....	Mild, simple secondary anemia, slight leucocytosis, and moderate lymphoid reaction.
3	8 mos.	7th mo.	Br. and art.	Moderate	Slight	0	0	Broncho-pneumonia	.....	Severe secondary anemia with leucocytosis and moderate lymphoid reaction.
4	9 mos.	6th mo.	Art.	Mild	0	Slight	0	0	.....	Moderately severe, secondary anemia with leucocytosis, a moderate lymphoid reaction and an occasional immature myeloid cell.
5	34 mos.	0	Br. and art.	0	Moderate	Moderate	Moderate	Otitis media	.....	Mild secondary anemia and leucocytosis, a moderate lymphoid reaction many immature lymphoid and a few immature myeloid cells.
6	20 mos.	9th mo.	Art.	Mild	0	Moderate	Moderate	Temp. 104° F. Unexplained	Blindness and idiocy	Severe anemia and marked lymphoid reaction with many immature cells of all types.
7	42 mos.	0	Br. and art. and mix.	Severe	0	Very Marked	0	0	Cystic kidneys	Moderately severe anemia, both leucopenia and leucocytosis, lymphoid reaction, and immature cells of all types.
8	6½ mos.	0	Br.	Very mild	0	Moderate	Moderate	0	.....	Very severe anemia, no leucocytosis, and immature cells of all types.
9	14 mos.	0	Br. and art.	Mild	Slight	Moderate	Moderate	Otitis media Varicella Diphtheria Impetigo	.....	Moderately severe anemia with leucocytosis, often very high, lymphoid reaction and immature cells of all types.
10	20 mos.	8th mo.	Br. and art.	Moderately severe	Slight	Marked	Slight	0	.....	Moderately severe anemia, no leucocytosis, slight lymphoid reaction, and immature cells of all types.

Enlargement of the lymph nodes was found in four cases, but was independent of the blood reaction, and the presence, absence, or amount of enlargement of the spleen and liver.

Enlargement of the spleen was a factor of greatest variation, varying from a spleen of normal size to those showing great enlargement. One could not predict from the size of the spleen what the blood picture would be, for severe anemia with immature cells was encountered with slight splenic enlargement, and simple anemia without abnormal cells occurred with a huge spleen. The fact that the degree of splenic enlargement could not be correlated with the severity of the rickets present may again be emphasized.

Enlargement of the liver was not marked in any case. When present, it was found with enlargement of the spleen; splenomegaly, however, occurred independently of hepatomegaly.

Various infections, so common in this class of patients, may have temporarily influenced the blood reaction, but in none of these patients could the anemia be attributed solely to infection. There was no peculiar type of blood reaction in them, nor any constancy in the degree of the enlargement of the spleen or lymph nodes.

Leucocytosis was a very variable feature and was in some cases apparently associated with an acute infection. The total number of leucocytes, however, bore no constant relationship to the other features of the case.

From the foregoing analysis of these cases it is seen that in infants with anemias, enlargement of the spleen is very common and is often very marked; and enlargement of the liver and lymph nodes is frequently encountered. The importance of this enlargement in diagnosis and prognosis is very much less than in the adult. In these cases great variation in the blood picture may occur. Although various grades of anisocytosis, poikilocytosis, basophilia and a relative increase in cells of the large mononuclear-transitional cell group are found in all, other qualitative changes vary markedly both in regularity of occurrence and degree of severity. The blood may show only the changes of a simple secondary anemia as seen in adults; it may show, in addition to this, different degrees of lymphocytosis sometimes so marked that the differentiation from lymphoid leukemia may be difficult at first; it may show the presence of immature blood cells of all types, the so-called von Jaksch's anemia; or it may present any gradation between these three major types. In the presence of any of these qualitative changes there may or may not be a leucocytosis. The occurrence of the different blood pictures appears to be wholly unrelated to the other findings. It is not possible to predict from the physical examination of the child what the character of the blood reaction will be. The type of reaction shown by the blood does not seem to be dependent upon the degree of anemia, the presence, absence, or severity of rickets, or to be influenced by prematurity or birth at term.

The reaction on the part of the infant with enlargement of the spleen, liver and lymph nodes, and with changes in the blood picture as described above constitutes a fairly definite symptom complex, peculiar to the first few years of life. This symptom complex has been given special names such as "infantile splenic anemia," anemia infantum pseudoleukemica," and "von Jaksch's anemia" and considered as a special disease or some atypical kind of leukemia. From examination of the case histories given above it would seem that this is not justified. This symptom complex has not been shown to be a disease *sui generis* and is not as yet entitled to a special name. Any name which suggests leukemia is especially unfortunate, for cases such as are presented above are not leukemic in any stage and bear no relationship to leukemia. Hence, the use of such names as "anemia infantum pseudoleukemica," and "von Jaksch's anemia" which by authority of his original publication implies a relationship to leukemia, should be discontinued. Whatever combination of anemia, total white blood cell count, differential formula, enlargement of the spleen, liver or lymph nodes is encountered in these cases, or whatever may be the relative severity of any one or more of these findings, the significance is the same and permits only the same interpretation. This symptom complex can best be interpreted as the peculiar type of reaction on the part of the infant to the presence of a factor producing secondary anemia.

The reason for the enlargement of the spleen, liver, and lymph nodes, a lymphocytosis, and the appearance of immature cells, both of the red and white blood cell series in the peripheral circulation, and the marked variation in the presence and degree of these signs so frequently encountered in infants with anemia is not clear. The fact that this symptom complex is found in association with so many different conditions (prematurity, severe nutritional disorders, rickets, tuberculosis, syphilis, malaria, leishmaniasis and other acute and chronic infections) would make it appear probable that these various manifestations are brought about by no special etiologic factor. It seems quite probable that the infantile hematopoietic system is more labile than that of adults, and that in the presence of an anemia, immature cells of all types enter the peripheral circulation more readily and the other changes mentioned are more easily brought about. If this be true, any etiologic agent which would produce in the adult merely a simple secondary anemia (reduction in the number of red blood cells and hemoglobin alone) may, in the infant, result in more severe and striking changes. The possibility must be also mentioned that these changes are brought about by the presence of some special factor or influence that is operative in infants but not in adults. Among the conditions peculiar to the period of life in which this symptom complex is observed, may be mentioned the immature state of the hematopoietic system accompanying premature birth, the peculiar dietetic influences present in infants, and rickets. Although we have shown that the symptom complex described is frequently seen in association with these conditions, we have no evidence that these peculiar conditions are entirely responsible for the reaction observed. Rickets, especially, or its underlying cause has been suggested by many as the etiologic agent in question. The evidence at hand, however, per-

mits us to state only that the two conditions (rickets and anemia) are frequently seen in association with each other. Whatever the underlying cause may be, the symptom complex which we have described remains a secondary anemia, peculiar only in the variability of the infantile response.

Conclusions

1. In infants with anemia, enlargement of the spleen is frequent, and enlargement of the liver and lymph nodes is fairly common. These findings alone are of no specific diagnostic or prognostic importance.

2. The infantile hematopoietic system frequently reacts to anemia with a relative lymphocytosis, by throwing out immature blood cells, or with both of these qualitative changes in varying grades of severity. Any of these reactions may be present with or without a leucocytosis, and may have no serious significance.

3. The presence, absence, or degree of splenomegaly, hepatomegaly, or general enlargement of the lymph nodes, the severity of the anemia, the total white blood cell count, or the type of qualitative changes in the blood, bear no constant relation to each other.

4. This symptom complex has not been shown to be a disease *sui generis* and all variations of it are probably merely an infantile response to some agent producing secondary anemia. It is not yet entitled to any special name, especially one that suggests a relationship to leukemia.

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PREGNANCY AND LABOR IN YOUNG PRIMIPARÆ

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In spite of the fact that most text-books of obstetrics contain little information upon the subject, there is a prevalent opinion that pregnancy and labor are attended by greater danger in young girls than in older women. Williams[1] differs from this view and states that labor in the girl of 16 or less is no more serious than in the women of more mature years. In order to test the correctness of this view I have collected and analyzed all labors in girls of 16 years of age or less which have occurred in the obstetrical service of The Johns Hopkins Hospital.

Varnier[2] has compared the average duration of labor in 100 primiparæ of less than 20 years of age with that in a similar number of patients between the ages of 20 and 30. He found the average duration was 13 hours, 5 minutes in the former as compared with 13 hours, 28 minutes in the latter. In all of the patients in both groups the pelvis was normal and the child presented by the vertex.

Gache,[3] of Buenos Aires, analyzed 91 cases of labor occurring in girls between the ages of 13 and 16. In 84 patients the pelvis was normal. Of the 91 patients, 78 were delivered spontaneously and 13 by operative measures. He estimated that the average duration of labor was 24 hours and that the children averaged 3039 grams in weight, and concluded that, so far as he could ascertain, the age of the patient is practically a matter of indifference.

Bondy[4] has reported 69 labors between the ages of 14 and 16, of which 12 resulted in the birth of premature children. In the 57 patients delivered at term he believed that labor was prolonged in 19 instances.

From the first 10,000 admissions to the obstetrical service of The Johns Hopkins Hospital I have collected the details of 500 labors occurring in girls between the ages of 12 and 16 inclusive. Since most of the abortions are admitted to the gynecological service, the few that appear in our records have not been considered, as they would give no accurate picture of the frequency of this complication.

Table 1 presents an analysis of the age at which delivery took place in each of the two races, and shows that there are more than twice as many blacks as whites in the series. As less than 45 per cent of all patients admitted to the service are blacks, this unusual predominance of colored young primiparæ may be regarded as an index of the incidence of precocious sexual relations in that race.

TABLE 1

Age	White	Black	Total
12	0	2	2
13	1	6	7
14	18	28	46
15	45	95	140
16	96	209	305
Total	160	340	500

Pelvis.—In every patient in the series the pelvis was measured both externally and internally and the results are shown in Tables 2 and 3.

In the 160 white patients contracted pelves were noted in 21, a percentage of 13.12. The generally contracted and the funnel were the most frequent types noted, making up 16 of the 21 cases.

Williams,[5] in a series of 1313 white women, irrespective of age, found that the incidence of contracted pelvis was 13.33 per cent, and stated that the funnel and the generally contracted were the two types most frequently encountered, the two making up 125 of his 175 cases. On comparing our figures with his, it is seen that the incidence of contracted pelvis is practically the same in both series, and that the types of pelvic contraction most frequently noted were identical. In other words, the white girl of 13 to 16 years of age has as large a pelvis as her older sister.

In the 340 blacks in our series the incidence of pelvic contraction was 60.58 per cent. The two most frequent types encountered were the generally contracted and the generally contracted rhachitic, the two making up 140 of our 206 cases. Williams[5] found 312 contracted pelves in 902 colored women of all ages, a percentage of 40.93. Of these the generally contracted and the generally contracted rhachitic made up 258 of his 312 cases. Thus it is seen that in colored young primiparæ contractions of the pelvis occur 50 per cent times more frequently than in colored women of more mature years. This is to be expected when it is remembered that casual observation seems to indicate that the black woman in Baltimore reaches physical maturity later than does the white. Our figures are in accord with those of Williams that the two types of contracted pelves most frequently noted in the black are the generally contracted and the generally contracted rhachitic.

Abnormal Pregnancy.—Table 4 shows the complications of pregnancy met with in the series of 500 cases.

TABLE 2

CLASSIFICATION OF PELVES IN 160 WHITE YOUNG PRIMIPARÆ

Age	Normal pelves	Contracted pelves					Total
		Generally contracted	Simple flat	Funnel	Gen. cont. funnel	Total cont. pelves	
13	1	0	0	0	0	0	1
14	14	1	0	2	1	4	18
15	37	5	0	2	1	8	45
16	87	3	2	3	1	9	96
Total.	139	9	2	7	3	21	160

TABLE 3

CLASSIFICATION OF PELVES IN 340 BLACK YOUNG PRIMIPARÆ

Age	Normal pelves	Contracted pelves								Total
		Generally contracted	Simple flat	Gen. cont. rhachitic	Flat rhachitic	Funnel	Gen. cont. funnel	Coxalgic	Total cont. pelves	
12	0	2	0	0	0	0	0	0	2	2
13	0	3	0	3	0	0	0	0	6	6
14	8	11	0	4	0	2	3	0	20	28
15	41	16	0	16	1	9	12	0	54	95
16	85	51	1	34	1	12	24	1	124	209
Total.	134	83	1	57	2	23	39	1	206	340

TABLE 4

ABNORMAL PREGNANCIES

	Preeclamptic toxæmia	Eclampsia	Nephritic toxæmia	Syphilis	Pyelo-nephritis	Typhoid	Measles	Total
White	2	9	1	1	0	0	0	13
Black	8	7	0	25	1	1	1	43
Total	10	16	1	26	1	1	1	56

At first glance it appears that there was an abnormally high incidence of preeclamptic toxæmia and eclampsia, 10

of the former and 16 of the latter. However, five of the cases of the former and 14 of the latter were not treated in the prenatal clinic but were referred to the service because of the existence of the disease. Consequently, no such incidence of these complications should be expected to obtain in the average run of young primiparæ.

It is noted that there were 26 cases of syphilis in the series, 25 being in black women and 1 in white. This is a much lower incidence of the disease than that reported from this clinic by Williams.[6] The discrepancy can be explained not only on the grounds that in the young girl syphilis would not be expected to be present so frequently, but also because of the fact that more than half of the patients in the series passed through our hands before the introduction of the routine Wassermann determination and, therefore, it may be assumed that many cases of infection escaped detection.

Premature Labor.—Of the entire series of 500 cases 58, or 11.6 per cent, terminated in premature labor. When divided according to race, it is seen that this termination occurred in 17 of the 160 whites and in 41 of the 340 blacks, an incidence of 10.52 and 12.05 per cent, respectively.

In the majority of cases in both races the cause of premature termination could not be determined. In the blacks syphilis was the most important ascertainable etiological factor, and it seems safe to surmise that, had the more recent methods of diagnosis been applied throughout the series, many of the cases classified as undetermined would have shown that syphilis was the causative factor.

TABLE 5

PREMATURE LABORS

	Undetermined	Syphilis	Eclampsia	Prem. sep. placenta	Twins	Monsters	Measles	Typhoid	Total
White .	11	1	2	0	2	1	0	0	17
Black..	24	11	1	2	1	0	1	1	41
Total ..	35	12	3	2	3	1	1	1	58

Duration of Labor.—Of the 442 patients delivered at term the duration of labor was accurately recorded in 430—138 whites and 292 blacks. The 12 remaining patients were delivered by Cæsarean section or *accouchement forcé* before the cervix had become fully dilated.

Tables 6 and 7 show the average duration of term labor in the two races. From Table 6 it is seen that the average duration of labor for the entire series of 138 white girls is 15 hours, 44 minutes. However, when the pelvis is normal the average falls to 15 hours, 10 minutes; on the other hand, when the pelvis is contracted, labor is 4 hours, 42 minutes, longer than when it is normal.

The average duration of labor in the 292 blacks is 16 hours, 40 minutes. This increase may be assumed to be due to the greater frequency of contracted pelves in that race; as, when the pelvis is normal, the average duration is 14 hours, 40 minutes, as compared with an average of 18 hours, 7 minutes, when the pelvis is contracted.

It is usually stated that the average duration of labor in primiparæ, irrespective of age, is 18 hours. G. Veit[7] places it at 20 hours. Accepting the lower figure as correct, it is seen that the young primipara has a labor shorter by 2 hours, 16 minutes in the white and 1 hour, 20 minutes in the black race.

TABLE 6

AVERAGE DURATION OF LABOR—WHITE

Age	Total		Normal pelvis		Contracted pelvis	
	No. cases	Average duration	No. cases	Average duration	No. cases	Average duration
13	1	10h. 12m.	1	10h. 12m.	0	0
14	15	20h. 02m.	11	18h. 48m.	4	23h. 24m.
15	40	15h. 15m.	33	15h. 27m.	7	14h. 15m.
16	82	15h. 16m.	76	14h. 35m.	6	24h. 06m.
Total....	138	15h. 44m.	121	15h. 10m.	17	19h. 52m.

TABLE 7

AVERAGE DURATION OF LABOR—BLACK

Age	Total		Normal pelvis		Contracted pelvis	
	No. cases	Average duration	No. cases	Average duration	No. cases	Average duration
12	2	18h. 03m.	0	0	2	18h. 03m.
13	5	17h. 20m.	0	0	5	17h. 20m.
14	25	19h. 44m.	8	18h. 50m.	17	20h. 10m.
15	82	16h. 48m.	39	13h. 53m.	43	19h. 27m.
16	178	16h. 09m.	75	14h. 43m.	103	17h. 15m.
Total....	292	16h. 40m.	122	14h. 40m.	170	18h. 07m.

More precise information as to the duration of labor may be gained by the "modal" method. This is shown in Tables 8 and 9. The shaded blocks represent the total number of term labors divided into groups of two hours each, while the lines represent the labors occurring in patients with normal pelves. Inspection of these tables shows that in both races the most frequent duration of labor in the entire series, as well as in those with normal pelves, is between 10 and 12 hours. Unfortunately, no comparable statistics concerning the duration of labor in older women are available, but it is not believed that they would show a shorter duration than that observed in young primiparæ.

It is interesting to note that, in spite of the much higher incidence of contracted pelvis in the blacks, the most frequent duration of labor is the same as for the whites. The explanation is, as will be shown later, that the babies of the former are smaller, and, therefore, are less likely to be disproportionate to the size of the pelvis.

Delivery.—Of the 442 deliveries at term, 379 were spontaneous and 63 were operative, an incidence of 85.74 and 14.26 per cent respectively. Of the latter 18 were in whites and 45 in blacks. Notwithstanding the apparently greater frequency of operative interference in the blacks, the determination of the percentage frequency shows that the incidence is approximately the same in both races, being 12.95 per cent for the whites and 14.85 per cent for the blacks.

TABLE 8

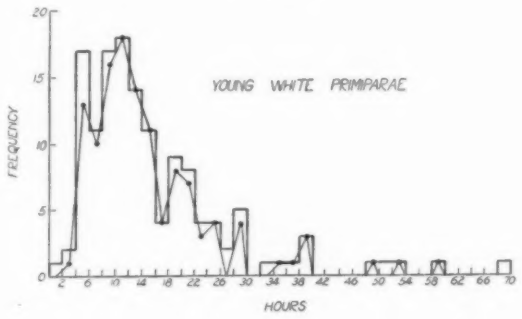
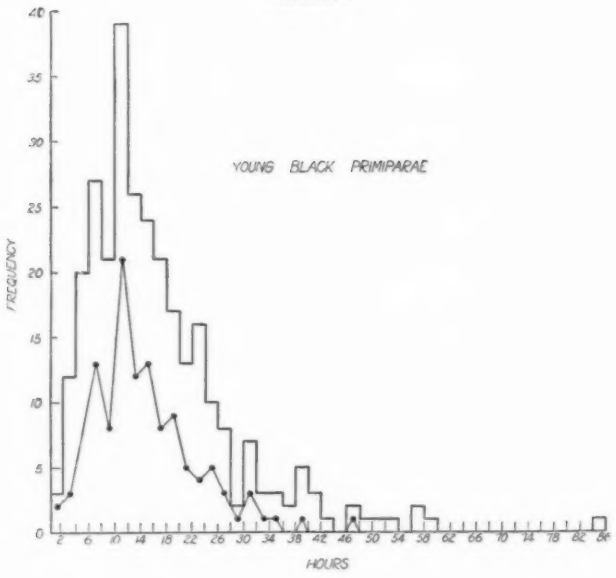


TABLE 9



Operations.—The types of operations are shown in Table 10. While the incidence of pelvic contraction was 60.58 per cent in the blacks, only 17 of the 45 operations were done because of pelvic dystocia. Of these, 10 were Cæsarean sections, 4 pubiotomies and 3 craniotomies. In the whites only two operations were necessitated by the pelvis, one Cæsarean section and one high forceps.

Weight of the Child.—In casting about for an explanation for the relatively short labor in very young primiparæ it seemed possible that it might be afforded by the smaller size of the children. Accordingly the material was studied from that point of view. Tables 11 and 12 show the average weight of the children in both races. In the series of 143 whites delivered at term the average weight of the children was 3181 grams. When classified according to the pelvis of the mother, the average in the 126 patients with normal pelves was 3200 grams, while in the 17 with contracted pelves it was 3045 grams, a difference of 155 grams in favor of the child born of a mother with a normal pelvis. The average weight of

TABLE 10

OPERATIONS

	Low forceps	Mid forceps	High forceps	Breach extraction	Version and extraction	Cæsarean section	Pubiotomy	Craniotomy	Accouch. forcé	Induction of labor	Total
White	7	3	2	3	0	1	0	0	0	2	18
Black	18	2	2	2	1	10	4	3	1	2	45
Total ...	25	5	4	5	1	11	4	3	1	4	63

TABLE 11

AVERAGE WEIGHT OF THE CHILDREN—WHITE

Age	Total		Normal pelvis		Contracted pelvis	
	No. cases	Av. weight	No. cases	Av. weight	No. cases	Av. weight
13	1	2700	1	2700	0	0
14	15	3063	12	3030	3	3199
15	42	3171	34	3213	8	2994
16	85	3106	79	3239	6	3037
Total....	143	3181	126	3200	17	3045

TABLE 12

AVERAGE WEIGHT OF THE CHILDREN—BLACK

Age	Total		Normal pelvis		Contracted pelvis	
	No. cases	Av. weight	No. cases	Av. weight	No. cases	Av. weight
12	2	2830	0	0	2	2830
13	5	3030	0	0	5	3030
14	24	3034	8	3211	16	2945
15	82	3043	39	3062	43	3025
16	186	2979	75	3042	111	2945
Total....	299	3004	122	3060	177	2966

the colored children born at term was 3004 grams—177 grams less than that in the whites. In the 122 blacks with normal pelves the average weight was 3060 grams, while it was 2966 grams in the 177 patients with contracted pelves—a difference of 94 grams.

Riggs,[8] in a report from this clinic, found the average weight of the children of 370 white and of 196 black primiparæ of

all ages was 3224 and 2996 grams respectively—a difference of 228 grams. The figure usually given as the average weight of term white children is 3250 grams. A comparison of our findings with this figure, as well as with those of Riggs, shows that the children of young primiparæ vary but little in weight from those born to older women. It is, therefore, evident that the relatively short labor of the young primipara cannot be explained on the ground that the baby is smaller than at a more advanced maternal age.

Maternal Mortality.—In our series of 500 patients there were four maternal deaths, a percentage of 0.8. All of these deaths occurred in colored girls. One died from eclampsia on the third day after the the spontaneous delivery of a term child. The other three patients were delivered of premature children, one by manual dilatation of the cervix and version and extraction because of prolonged labor and intrapartum infection. She died suddenly two hours later, with a clinical diagnosis of hæmorrhage and shock, but the findings at autopsy were negative. Of the other patients one died on the fifth day of the puerperium from streptococcus peritonitis and the other on the tenth day from pyelonephritis which had existed for weeks before delivery.

TABLE 13

FŒTAL MORTALITY

	Toxæmia	Syphilis	Cause not determined	Asphyxia	Destructive operations	Infected cord	Pneumonia	Total
White	3	2	4	2	0	1	1	13
Black.....	3	4	4	1	4	1	1	18
Total	6	6	8	3	4	2	2	31

Fœtal Mortality.—Of the 442 deliveries at term, 31 children were stillborn or died within the first two weeks of life, a percentage of 7.0. The causes of death are shown in Table 13.

CONCLUSIONS

Based upon the study of the 500 patients comprised in this report, it seems permissible to conclude that pregnancy and labor are attended by no greater danger in the young primipara than in the older woman. On the other hand, the duration of labor is actually shorter. As our figures show that the size of the children is not inferior to that noted in older women, and that abnormal pelves occur quite as frequently, this result must be attributed to the greater elasticity of the soft parts. Consequently, speaking from a purely obstetrical point of view, the ages under consideration appear to be the optimum time for the occurrence of the first labor.

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THE PROTECTIVE POWER OF SERUM IN PERNICIOUS ANEMIA AND OTHER CONDITIONS AGAINST HEMOLYSIS BY SAPONIN AND BY SODIUM OLEATE

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It is a well-known fact that human serum has the power to protect against hemolysis by many different hemolytic agents. In studies of the protective power of human serum against hemolysis by one of them, sodium oleate, it was found that this antihemolytic property was diminished in the serum from patients suffering from hemolytic anemia and from those in whom involvement of the liver and spleen in the disease process was a prominent feature.[1] The experiments establishing this point were undertaken with the idea that hemolysis in the hemolytic anemias might be due to a diminution in protective power of serum against a hemolysin normally circulating in the blood. For this reason sodium oleate was used as the hemolytic agent because it is a substance which may readily be supposed to be present in the body under normal conditions. In view of these findings with sodium oleate it was thought wise to study also the protective power of serum against a hemolytic agent not present in the body and to compare the results with those obtained with sodium oleate. Saponin is a hemolysin against which serum has marked protective power and one which has not been demonstrated in the body. Accordingly, the experiments to be reported below were a study of the protective power of serum against saponin, a hemolytic agent not present in the body, and sodium oleate, one which probably is present normally.

Several observations of interest in relation to the hemolytic power of saponin and its inhibition by various substances have been reported. Wacker [3] noted that extracts from the stomach and intestinal mucosa inhibited the hemolytic action of saponin, and Frei [5] that a similar action was exerted by hemoglobin solution. In his experiments Frei used hemoglobin from dog's corpuscles. Noguchi [4] added the dyes eosin and erythrosin to saponin and found that by this treatment its hemolytic power was diminished. He also reported [5] that, if red blood corpuscles were exposed to cobra-venom beforehand, their resistance to hemolysis by saponin was increased. Arrhenius [6] recorded a similar increase in resistance to hemolysis of red blood cells that had been exposed to lecithin and to sodium oleate. Heuberger and Stepp [7] tested the resistance to hemolysis by saponin of washed red blood cells from patients suffering from many diseases; the tables recorded show considerable variability of resistance in the different conditions studied. The least resistant cells were those from cases of pernicious anemia, and among the next resistant were those from patients with severe anemias. May [8] expressed the opinion that variations in the resistance of red blood cells to hemolysis by saponin depended upon modifications in the relative proportions of lecithin and cholesterin in the cell. This investigator found that in pulmonary tuberculosis and typhoid fever the resistance of the red blood cells was diminished; and in icterus, in various types of nephritis, and in arteriosclerosis the resistance might be either increased or diminished. In pernicious anemia and in cancer showing a blood picture somewhat resembling that of pernicious anemia, May reported the resistance of the red blood cells to hemolysis by saponin to be the same as that from normal people. He concluded, therefore, that anemias were not due to increased fragility of the red blood cells. Ransom [9] showed that not only in serum, but in the stroma of the red blood cells also, there was a substance capable of inhibiting hemolysis by saponin and identified this substance definitely as cholesterin. In this same report Ransom stated that cholesterin protected effectively against saponin hemolysis, and that lecithin did not. This latter observation is not in accord with the findings of Clark and Evans [10] who reported that lecithin exerted some protective power against hemolysis by saponin, although it was much less potent in this regard than cholesterin. Of more immediate interest in relation to the points under investigation in this study are the findings of Port.[11] He measured quantitatively the protective power of human serum against hemolysis of human red blood cells by saponin and reported that the extent of this antihemolytic power of the serum was remarkably constant in normal persons and in patients suffering from a wide range of diseases. It was found to be increased in the lipemia of diabetes, in different kinds of nephritis, in lues and in typhoid fever. In three cases of pernicious anemia tested, however, the antihemolytic power of the serum showed a marked diminution; and to be compared with this is the normal antihemolytic value found in the serum from a case with a severe secondary anemia showing 1,000,000 red blood cells. The findings reported by Abderhalden and Weil,[12] who tested the antihemolytic property against saponin of horse serum, are also of interest. They found a slight diminution in protective power in the serum from horses suffering from glanders and septic anemia, and a severe diminution in the serum of all horses having so-called "pernicious anemia." No other disease was found in which the reduction in antihemolytic power of the serum against saponin was great enough to compare with that in "pernicious anemia" and it was suggested, therefore, that this finding could be used as a diagnostic test.

In the investigations reported in this paper quantitative measurements were made of the protective power of human serum against hemolysis of guinea-pig corpuscles by saponin. The saponin used was a chemically pure specimen furnished by the Heyl Laboratories of Chicago, and taken just before use from the same 10-ounce bottle in which it was delivered. At the same time quantitative measurements of the antihemolytic property of the serum against sodium oleate were made. The technique employed and control experiments carried out were the same as already reported [1] in studies of the protective power of serum against hemolysis by sodium oleate, except that the dilutions of saponin were not so great as those for sodium oleate. A number of tubes, each containing 2 c. c. of a different dilution of hemolytic agent were set up in series and to each 0.25 c. c. of the serum to be tested for protective power against hemolysis was added. This was heated at 37° C. in the water-bath for half an hour, cooled for half an hour, and then 0.25 c. c. of a 0.75 per cent suspension of washed guinea-pig cells was added as indicator. This preparation was incubated at 37° C. in the water-bath for two hours, allowed to sediment in the ice-box for one hour, and then a reading of hemolysis was made. In the experiments with sodium oleate the tubes carried dilutions of the hemolytic agent of 1-45,000 to 1-100,000 in steps of 5000: *i. e.*, 1-45,000, 1-50,000, 1-55,000, 1-60,000, etc. In such a series normal serum regularly protected guinea-pig cells against hemolysis up to strengths of 1-45,000 to 1-55,000 of sodium oleate, so that any hemolysis in the tubes containing solutions of sodium oleate weaker than 1-55,000 might be considered as indicating a diminution in the protective power of the serum being tested against hemolysis by sodium oleate. Preliminary experiments with saponin, however, indicated that to obtain comparative results different dilutions of this hemolytic agent must be employed. For example, when the hemolytic power of saponin was tested with unprotected guinea-pig cells the following results were obtained:

Highest dilution showing	Some hemolysis	Complete hemolysis
Guinea-pig 1	1-140,000	1-40,000
Guinea-pig 2	1-140,000	1-40,000
Guinea-pig 3	1-160,000	1-40,000

Earlier experiments with sodium oleate, in which the same technique was employed, showed:

Highest dilution showing	Some hemolysis	Complete hemolysis
Guinea-pig 1	1-170,000	1-110,000
Guinea-pig 2	1-140,000	1-110,000

From these findings one may conclude that saponin is a weaker hemolytic agent than sodium oleate, for although the highest dilutions showing some hemolysis were essentially the same with both, complete hemolysis occurred with much weaker solutions of sodium oleate than of saponin. This difference in hemolytic power of sodium oleate and saponin was also pronounced in the preparations in which the guinea-pig corpuscles were protected by serum as in the technique used regularly in titrating the antihemolytic power of serum. As already noted, normal* serum protected against hemolysis of sodium oleate up to strengths of 1-45,000 to 1-55,000. With saponin, however, the highest dilutions in which hemolysis was seen in the presence of normal serum were 1-18,000, 1-20,000 and 1-22,000 (Table I).* Accordingly, in the experiments with saponin, the tubes of each series contained dilutions of 1-18,000 to 1-32,000 in steps of 2000, and if any hemolysis was seen in tubes containing solutions of saponin weaker than 1-22,000 it was considered as indicating a diminution in the protective power of the serum being tested against hemolysis by this agent.

Using the technique outlined in a previous paper,[1] we tested the protective power of the serum from a number of patients against hemolysis by saponin and sodium oleate. The results appear in Tables I, II and III.

The figures recorded in Table I are those obtained with serum from normal persons. Under Case 16 of this table are the figures for several titrations made on the same person at different times. The constancy in the degree of protective power of normal serum from different persons and from the same person at different times against hemolysis by saponin is noteworthy, and corresponds in this regard with that found

* These findings suggest the possibility that saponin is not only a weaker hemolytic agent than sodium oleate, but also that human serum may protect more strongly against saponin than against sodium oleate.

TABLE I

RESULTS OF THE TITRATION OF SERA FROM NORMAL PERSONS FOR PROTECTIVE POWER AGAINST HEMOLYSIS OF GUINEA-PIG CORPUSCLES BY SAPONIN AND SODIUM OLEATE

Number	Date	Highest dilution of *saponin* showing hemolysis	Highest dilution of *sodium oleate* showing hemolysis
1	5- 5-20	20,000	.....
2	5-17-20	20,000	.....
3	5-21-20	20,000	55,000
4	5-26-20	20,000	50,000
5	6- 9-20	20,000	50,000
6	6-16-20	20,000	.....
7	7- 7-20	20,000	.....
8	7-17-20	18,000	50,000
9	7-24-30	20,000	55,000
10	12- 8-20	18,000	.....
11	12-23-20	18,000	55,000
12	12-30-20	20,000	.....
13	1- 7-21	22,000	50,000
14	1-12-21	22,000	55,000
15	1-14-21	20,000	45,060
16	1-19-21	20,000	55,000
..	1-22-21	18,000	.....
..	1-26-21	20,000	.....
..	1-31-21	20,000	.....
..	2-12-21	20,000	55,000
..	2-16-21	20,000	55,000

TABLE II

RESULTS OF THE TITRATIONS OF SERA, FROM PATIENTS HAVING NEITHER PERNICIOUS ANEMIA NOR LIVER-SPLEEN SYNDROME, FOR PROTECTIVE POWER AGAINST HEMOLYSIS OF GUINEA-PIG CORPUSCLES BY SAPONIN AND SODIUM OLEATE

No.	Name	R. B. C.	R. B. C.	Hb. %	W. B. C.	P. M. N. %	Highest dilution of *saponin* showing hemolysis	Highest dilution of *sodium oleate* showing hemolysis	Diagnosis and remarks
1	P. G.	1-26-21	2,464,000	35	5000	73	26,000	75,000	Secondary anemia. Bleeding duodenal ulcer.
2	E. B. P.	1-28-21	4,504,000	50	13,600	75	20,000	70,000	Chronic infectious arthritis.
3	N. D.	1-25-21	4,320,000	77	7780	52	26,000	70,000	Cerebral hemorrhage. Old mastoiditis.
4	E. R. B.	1-31-21	4,848,000	100	6080	80	20,000	55,000	Hysteria; paralysis of left side.
5	J. R. S.	1-29-21	5,604,000	85	6560	58	24,000	65,000	Pleurisy; probably tuberculosis.
6	T. S.	2-10-21	4,032,000	76	7960	57	22,000	70,000	Luetic aortitis.
7	S. M.	2- 5-21	5,664,000	100	7500	..	22,000	60,000	Cerebro-spinal lues.
8	H. B.	2- 7-21	4,842,000	78	8800	76	20,000	60,000	Arteriosclerosis and nephritis.
9	R. T.	2-15-21	4,072,000	63	2880	76	24,000	55,000	Empyema.
10	G. G.	2-15-21	2,928,000	42	7400	60	28,000	70,000	Sporotrichosis.

TABLE III

RESULTS OF THE TITRATIONS OF SERA FROM PATIENTS WITH PERNICIOUS ANEMIA OR LIVER-SPLEEN SYNDROME FOR PROTECTIVE POWER AGAINST HEMOLYSIS OF GUINEA-PIG CORPUSCLES BY SAPONIN AND SODIUM OLEATE

No.	Name	Date	R. B. C.	Hb. %	W. B. C.	P. M. N. %	Highest dilution of *saponin* showing hemolysis	Highest dilution of *sodium oleate* showing hemolysis	Diagnosis and remarks
1	A. T.W.	5-21-20	2,352,000	48	12,200	..	26,000	95,000	Hemolytic icterus.
		2- 9-21	3,400,000	65	13,000	..	32,000	80,000	
2	J. H.W.	1-19-21	2,028,000	34	3,380	47	28,000	90,000	Primary aplastic anemia.
3	A. C.	1-26-21	.....	..	.....	..	26,000	90,000	Cirrhosis of liver.
		2- 4-21	2,722,000	50	4,200	76	30,000	95,000	
		2-12-21	.....	..	....	..	22,000	90,000	
		2-19-21	3,372,000	69	2,700	..	32,000	100,000	
4	W. D.	1-28-21	1,896,000	29	5,250	91	28,000	90,000	Myeloid lukemia of skin.
		2- 2-21	1,544,000	29	9,850	97	26,000	95,000	Figures in P. M. N. % column include a few myelocytes.
5	H. H.C.	7- 3-20	1,032,000	40	3,600	..	20,000	65,000	Pernicious anemia. Has had repeated transfusions.
		7-11-20	1,536,000	36	2,600	53	26,000	80,000	
		7-18-20	2,200,000	42	2,400	..	30,000	85,000	
6	A. J. K.	7- 3-20	.....	..	.....	..	20,000	70,000	Pernicious anemia.
		7-11-20	1,760,000	28	3,400	..	20,000	55,000	
		7-18-20	1,888,000	29	3,000	..	30,000	85,000	
7	W. A J.	6-13-20	2,436,000	53	3,720	59	32,000	70,000	Pernicious anemia.
		7- 3-20	3,400,000	78	4,000	45	20,000	65,000	
8	F. T. H.	5-23-20	614,000	16	32,000	46	28,000	65,000	Pernicious anemia. Acute infection.
9	W. H.P.	7-15-20	2,952,000	68	4,000	86	30,000	90,000	Pernicious anemia.
10	C. H.	7-15-20	1,700,000	45	3,500	57	22,000	70,000	Pernicious anemia.
11	J. J.	1- 7-21	1,280,000	35	8,750	58	22,000	50,000	Pernicious anemia.
12	W. B	1-15-21	2,256,000	56	4,840	57	22,000	70,000	Pernicious anemia.
		1-20-21	3,384,000	47	2,120	24	32,000	85,000	Transfusion 1-18-21.
		2- 4-21	1,516,000	35	1,660	25	32,000	100,000	Transfusion 1-21-21, followed by a severe serum reaction.
		2- 9-21	1,608,000	34	4,640	90	32,000	95,000	
13	F. K.	1-14-21	1,696,000	39	7,240	63	20,000	55,000	Pernicious anemia. Patient is in very good shape. Last seen 30 months ago and has been well since.
14	J. W. B.	1-22-21	.....	..	.....	..	32,000	100,000	Pernicious anemia. In aplastic stage.
15	D. B. L.	2- 7-21	1,208,000	28	6,400	66	30,000	95,000	Pernicious anemia. There was also a positive Wassermann reaction which became negative after salvarsan therapy.
		2-15-21	1,000,000	22	6,080	58	28,000	70,000	
16	F. S.	1-26-21	992,000	20	3,800	63	26,000	70,000	Pernicious anemia.
		1-31-21	784,000	20	3,940	67	30,000	90,000	
		2- 4-21	2,144,000	33	1,920	64	30,000	80,000	
		2- 9-21	1,464,000	33	2,800	66	32,000	80,000	
		2-16-21	1,576,000	35	2,600	54	32,000	75,000	
17	E. M.	1-26-21	4,000,000	75	5,080	55	20,000	60,000	Pernicious anemia. Patient has been in good shape for years. Symptoms primarily of C. N. S.

against hemolysis by sodium oleate at this time and previously noted. It will be noticed, however, that a serum may show with one hemolysin the highest antihemolytic titer ever seen with normal serum, and the lower limit of normal with the other. This probably means minor variations in the hemolytic power of the hemolytic agents as made up from day to day. On the other hand, it may mean slight variations in the antihemolytic power of normal serum; and if so, it suggests that this property of serum is due to a different substance in it for each hemolysin, and that these vary independently of each other. No definite statement may be made, but it appears likely that both of these factors are operative in this connection.

The figures recorded in Table II are those obtained with the sera from patients having either no anemia, a slight anemia, or a severe anemia associated with various diseases. All patients in this list, except No. 4, were very ill at the time the serum was tested. None had pernicious anemia or any evidence of involvement of the liver or spleen in the disease process present. The degree of protective power against saponin shown by the serum varied somewhat in these patients, and some reduction was common, although in the cases tested it was not severe. The degree of antihemolytic power was diminished against either sodium oleate or saponin in all except one of these sera. It was not, however, the same at all times for both hemolysins. Four cases showed normal protective power against hemolysis by saponin and some diminution against hemolysis by sodium oleate; and one case showed slight diminution in protective power against hemolysis by saponin and normal antihemolytic power against sodium oleate. The sera of five of these patients showed a normal protective power against hemolysis by saponin; and with sodium oleate two had a normal antihemolytic power and three had only a minimal degree of diminution. So, although the serum of a patient may not show the same degree of antihemolytic power for both sodium oleate and saponin, in general it may be said for saponin, as already reported for sodium oleate, that a diminution of antihemolytic power may or may not be present in this class of cases; and that, when present, it is not severe.

The figures recorded in Table III are those obtained with the sera from patients with the type of disease in which a marked diminution in protective power against hemolysis by sodium oleate had been previously found, namely, those suffering from hemolytic anemia or conditions in which changes in the spleen or liver are prominent features. In the sera from these patients the degree of antihemolytic power for saponin varied markedly among different individuals and also varied in the same individual at different times. A severe diminution in protective power against saponin was present in all but four of these cases, and was found at one time or another in every case tested more than once. Three of the four cases which showed normal antihemolytic power for saponin had normal values for sodium oleate also, and in the fourth case the diminution in protective power against hemolysis by sodium oleate was slight. All the cases which showed diminution in protective power against saponin had a diminution in antihemolytic power for sodium oleate. In many instances the degree of diminution in protective power against the two hemolytic agents was not the same; but when there was a severe reduction for one hemolytic agent, there was always some reduction for the other, usually quite pronounced.

When the antihemolytic values of the sera from the cases presented in Table II are compared with those in Table III, marked differences are apparent. The serum from none of the cases in Table II permitted hemolysis by saponin in dilutions greater than 1 to 28,000, or by sodium oleate in dilutions greater than 1 to 75,000. Among the 17 cases in Table III, however, 10 showed hemolysis by saponin in dilutions greater than 1 to 28,000, and 11 hemolysis by sodium oleate in dilu-

tions higher than 1 to 75,000. The averages of figures obtained in titration for protective power of serum found in the three classes of patients appear in Table IV. In Table V the results

TABLE IV

AVERAGES OF THE TITRATION VALUES OF ANTIHEMOLYTIC POWER FOR SAPONIN AND SODIUM OLEATE OF SERA FROM: (1) NORMAL PERSONS; (2) PERSONS WITH HEMOLYTIC ANEMIA OR LIVER-SPLEEN SYNDROME; (3) OTHER PATIENTS TESTED

	Number of titrations	Highest dilution of saponin showing hemolysis	Highest dilution of sodium oleate showing hemolysis
Normal persons	21	19,800	52,500
Patients with hemolytic anemia or spleen-liver syndrome.	35	27,085	80,000
Other patients	10	23,200	65,000

TABLE V

TABULATION OF THE SERA FROM THREE CLASSES OF PATIENTS: (1) NORMAL PERSONS; (2) PATIENTS WITH HEMOLYTIC ANEMIA OR LIVER-SPLEEN SYNDROME; (3) OTHER PATIENTS TESTED; ACCORDING TO THEIR ANTIHEMOLYTIC POWER FOR: (A) SAPONIN; (B) SODIUM OLEATE

A—SAPONIN

Dilutions of saponin	18,000	20,000	22,000	24,000	26,000	28,000	30,000	32,000	Total
Normal persons	4	15	2	...	...	...	...	...	21
Hemolytic anemia or spleen-liver syndrome	...	6	4	...	5	4	7	9	35
Other patients	...	3	2	2	2	1	...	...	10

B—SODIUM OLEATE

Dilutions of sodium oleate	45,000	50,000	55,000	60,000	65,000	70,000	75,000	80,000	85,000	90,000	95,000	100,000	Total
Normal persons	1	4	7	...	...	...	...	...	...	...	...	...	12
Hemolytic anemia or spleen-liver syndrome	...	1	2	1	3	6	1	4	3	6	5	3	35
Other patients	...	...	2	2	1	4	1	...	...	...	...	...	10

of all the titrations appear in summary. From these tables it is seen that the type of patient in which the serum shows the most severe reduction in antihemolytic power for saponin is the same as that in which the most severe reduction in antihemolytic power for sodium oleate is encountered.

The variations in antihemolytic power for saponin of sera from patients with hemolytic anemia did not run parallel with changes in the blood picture. It was noteworthy, however, that regardless of the degree of anemia present when the titration was done, when the antihemolytic power of the serum was high, the patient regularly said he was feeling better, and when a low antihemolytic titer was found, the patient complained of feeling badly. This same observation is true for variation in the antihemolytic power of serum from these patients for sodium oleate, and was made also in our earlier study when this hemolysin was used.

In summary, the following facts have been demonstrated in these experiments in which quantitative measurements were made of the protective power of human serum against hemolysis of guinea-pig cells by saponin and sodium oleate.

A. SAPONIN

1. The protective power of serum from normal persons against hemolysis by saponin is remarkably constant in degree.

2. In many diseases with anemias of various grades and types the protective power of the serum against hemolysis by saponin is diminished.

3. The decrease in protective power against hemolysis by saponin is most marked in anemias which are hemolytic in character and in other conditions in which involvement of the liver and spleen is a prominent feature in the disease process. In this class of cases, the diminution is very striking, both in degree and the regularity with which it is found. It varies markedly and seems to parallel more closely the general condition of the patient than the blood picture at the time the titration is done.

B. SODIUM OLEATE

1. When the protective power of human serum against hemolysis by sodium oleate is measured quantitatively, variations are found as when saponin is used as the hemolytic agent. Although the degree of antihemolytic power of one serum is not always exactly the same for both hemolytic agents, in general it may be said, in regard to types of patients, that the variations found with sodium oleate are the same as those with saponin.

CONCLUSIONS

The sera of patients with hemolytic anemia and other conditions in which the liver and spleen are prominently involved in the disease process, as compared with the sera of normal persons and of patients not suffering with either of these maladies, show a marked diminution in protective power against hemolysis by saponin, and by sodium oleate. Saponin is a hemolytic agent foreign to the body, and sodium oleate is one that is probably present in the body normally.

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THE ESTABLISHMENT OF COLLATERAL CIRCULATION FOLLOWING LIGATION OF THE THORACIC DUCT

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The general physiology of the lymphatic system has been studied from various angles. The discovery of the lymphatic system by Asellius[1] in 1627 was due to an observation correlating digestion with the activity of lymphatic vessels. Clinical pathological findings stimulated individuals to wound the thoracic duct in the chest and study the subsequent phenomena (Lower[2]); while others (Flandrin,[3] Colin[4]) ligated the thoracic duct in the neck and observed the influence of this procedure on the animal economy. Later when the knowledge of chemistry became advanced, thoracic duct fistulæ were made with a view toward studying the fluid in the duct under ordinary conditions and as modified by the digestion of various foods, *e. g.*, fats. Again, through the work of Heidenhain[5] and Starling,[6] the effects of lymphagogues of various classes were investigated. Finally, the thoracic duct was studied in regard to its power of supplying blood cells, chiefly small lymphocytes, to the blood stream (Biedl and v. Decastello[7]).

In this report an attempt has been made to review the literature of the experimental ligation of the thoracic duct, and also to give a description of a new method for ligating that vessel.

REVIEW OF LITERATURE

Probably the first one to attempt the ligation of the thoracic duct was Duverney[8] in 1675. He ligated the subclavian vein near the entrance of the duct, in some cases applying the ligature proximally and in others distally to the entrance. The dogs lived for a fortnight.

Sixteen years later in 1691, Flandrin,[3] a well-known veterinarian of his time, chose to repeat the work of Duverney, but preferred the horse, since he considered the lymph vessels in the smaller animals as too inconstant in their location. In the first experiment the animal died at the end of three days; subsequent dissection showed nothing of particular interest. In the second case a young horse was used. It experienced no ill effects immediately following the operation, nor in the subsequent 15 days during which it was allowed to live. "Perfect suppuration" took place in the wound, and with the possible exception of a distension of the thoracic duct at its point of ligation, the autopsy revealed no marked difference in the appearance of the lymphatics. Similar results were obtained with 10 more horses; the majority of the animals were killed 15 days following ligation, and the only abnormal finding was a distension of the thoracic duct at its point of ligation, with occasional extension of this distension down into the chest. One animal was kept for two and a half months after operation, and at autopsy showed a cicatrized thoracic duct. It is also interesting to note that Flandrin was among the first to introduce a cannula into the thoracic duct for the purpose of studying the properties of the lymph. He concluded that the lymph reaches the blood-stream through other channels than the thoracic duct.

In 1798 Sir Astley Cooper[9] reported the results of some experimental work involving the ligation of the thoracic duct in dogs. He was stimulated to undertake the experiments because he had observed three cases of obstruction to the thoracic duct in man. In two of these cases he found evidence of collateral circulation; in the third case no such evidence was found. In the first experiment the dog died 48 hours after the duct had been tied; dissection showed the viscera obscured by an effusion of chyle; particularly was this the case with the pancreas and the kidney; a small quantity of chyle had extravasated into the peritoneal cavity; the lacteals were empty; the thoracic duct was twice its normal size. These findings Cooper explained on the basis of a ruptured cisterna chyli. The second experiment was a great deal like the first, only the dog lived 2 days longer. The autopsy findings were the same; the cisterna chyli had burst and the extravasation had hidden entirely the aorta and the vena cava. In a third experiment the thoracic duct was cut and allowed to drain into the tissues; the animal died on the fourth day; dissection showed a pouch of lymph in the wound. These experiments were repeated always with the same results; no animal survived the tenth day. In one case Cooper noticed that a branch of the thoracic duct went over to the right trunk; also that the amount of extravasation bore a direct relation to the amount of food which the animal had just previously taken. Cooper did not give any evidence, *e. g.*, by injections, to support his belief that the cisterna had ruptured.

The only other investigator besides Cooper to report rupture of the cisterna chyli following ligation was Mayer.[10] Contrariwise, Rogers[11] observed no ill effects from ligation.

In 1821, Magendie[12] reported the experiments which Dupuytren made on several horses. Dupuytren ligated the thoracic duct in the neck, and observed that some animals died at the end of five to six days; while others did not seem to be affected by the operation. Subsequent injections showed that in the animals that died there was a complete obstruction of the thoracic duct; whereas, in those that survived—and one case was allowed to go for six weeks—a collateral circulation was always demonstrable. Accordingly, it was argued that the death of those animals that lived only five to six days, and in which the duct was tied, was due to the deprivation of nourishment furnished via the thoracic duct; and the only reason that the other animals lived longer was because collaterals to the thoracic duct had formed and had thus transmitted the necessary food substances to the blood stream.

Leuret and Lassaigne[13] tied the thoracic duct in the neck of a dog and found that the animal lived perfectly well, even gained weight. At the end of 58 days it was sacrificed at the height of digestion; dissection showed that the canal had been satisfactorily ligated. The only findings of importance were that the duct, the cisterna and the mesenteric lymphatics contained a small amount of chyle; and that the mesenteric veins seemed larger than normal. They believed that the chyle took an abnormal course to reach the blood, and that this path was from the cisterna chyli to the portal vein. They proved this assertion to their own satisfaction when they ligated the portal vein and found blood in the cisterna chyli and at the commencement of the thoracic duct. They also found that when the blood and chyle were taken from the thoracic duct and allowed to stand, two distinct clots were formed: the one, red, remained below; while the other, pink, evidently chylous, remained above.

Colin[14] in 1873 reviewed briefly and analyzed to some extent the work of the above mentioned investigators and then related his own experiences with ligations of the thoracic duct in various animals. All ligations seem to have been done in the neck. His first experiment was on a bull. The animal made an uneventful recovery and was sacrificed at the end of six or seven weeks when it was found that the thoracic duct was obliterated to the extent of five or six centimeters below the point of ligation, but that collaterals had formed at this point and had extended to the regular entrance of the thoracic duct into the veins. He repeated these experiments on two cows, taking care to include in his ligations all branches of the thoracic duct, and found at the end of 24 hours that there was a marked distension of the lymphatic system, as well as an extensive extravasation into the mesentery. He believed that the animals would have died from the operation if they had been kept long enough. On a bull 18 months old ligation resulted in death at the end of nine days; lymph did not reach the veins. After the completion of these observations on these large animals he made use of dogs for further experiments. One dog died from chylothorax on the day following the operation. Two other dogs died at the end of 20 and 25 days respectively, having refused food for almost the entire time. In both cases the thoracic duct was thickened and obliterated at its upper end and injections did not reach the veins. These animals "died the death of starvation." Colin concluded that ligation of the thoracic duct was not always followed by the same results. In those cases in which the duct was double, or anastomosed with the right thoracic duct, lymph reached the blood stream, and the animal recovered; whereas, if the duct were single and when ligation had been complete, death resulted promptly. He called the attention of future investigators to the fact that the entrance of the thoracic duct into the veins is so variable that in some cases it is absolutely impossible to prevent the lymph and chyle from reaching the blood stream.

However, Schmidt-Mühlheim[15] devised an operation which seemed to take care of all possible variations of the entrance of the thoracic duct into the veins. The problem which Ludwig gave Schmidt-Mühlheim was to establish whether the digestion products of albumen reached the blood stream via the thoracic duct or not. From this it can be readily seen what an exaggerated importance physiologists up to that time attached to the thoracic duct. He used dogs for his experiments and operated without an anesthetic or curare. He must be credited, however, with using strict aseptic technique during the operation, and, accordingly, ranks among the first to observe aseptic measures on experimental animals in the solution of biochemical problems. The operation consisted in isolating and tying off successively, on the right side as well as on the left, the v. jugularis externa, v. jugularis interna, v. axillaris and v. anonyma. Also the two thoracic ducts, right and left, were cut between ligatures. The operation did not affect the general condition of the animals in any particular; but since they were sacrificed at the end of six or seven days, no report of the effect of long continued ligation of the thoracic duct on the health of the animal is available. The complete occlusion of the entrance of the thoracic duct into the veins of the neck was demonstrated immediately after death by the injection of Berlin blue into the cisterna chyli at a pressure of 40-50 mm. of mercury; this was followed by dissection of the duct to the point of ligation. Again, the superior vena cava was also opened and a search made for evidence of the dye. Only those cases in which complete obstruction had been established were considered satisfactory; and following careful chemical analysis Schmidt-Mühlheim concluded that in complete obstruction to the chyle-flow into the blood vascular system, the digestion and absorption of albumens, as well as their conversion into urinary products, are the same as when the chyle is unobstructed in its passage to the blood stream. This result was an advance in the field of physiological chemistry.

The autopsy findings in these experimental dogs differed particularly in one essential respect from the observations of Cooper.[9] Cooper, it will be remembered, found rupture of the cisterna chyli following ligation with extensive extravasations; however, he failed to verify the rupture by injections.

Schmidt-Mühlheim, on the other hand, convinced himself by injecting directly into the cisterna with a solution of Berlin blue at a pressure of 40-50 mm. of mercury, and keeping this pressure up for hours that, in spite of wide extravasation, the cisterna chyli was intact; in no case was any dye found in the perivascular tissue. Marked distension of the lymphatics, chiefly abdominal, as well as enlargement of the lymph glands, was observed constantly. Also, it was noted, that a retrograde injection of the large lymphatic trunks emptying into the cisterna was possible to the extent of 3-4 cm., because the valves had become incompetent; particularly was this true of lymphatics coming from the liver. On the contrary, a retrograde injection of smaller lymphatics was never possible. He added that the mucosa of the intestine always had a normal appearance.

In 1883 Boegehold [15] reviewed the important work done on the thoracic duct. He reviewed not only the anatomy with its numerous variations, the physiology, the pathology, and clinical features involving the thoracic duct, but also gave an account of the experimental work done on the thoracic duct, adding the results of some of his own experiments. He was interested in studying the effects of wounds of the thoracic duct, and to that end cut the thoracic duct partially or entirely in the chest of dogs. He found that cutting about one-quarter of the periphery of the duct led to fibrin formation and clotting at the damaged area; cutting completely across the duct caused chylothorax and death; wounding the duct slightly, after it had been tied off effectually in the neck according to the method of Schmidt-Mühlheim,[12] resulted at the end of three days in a small amount of fibrin formation at the point of injury. Accordingly, he argued that absolute integrity of the thoracic duct was not essential to life. This was shown also by a number of clinical cases that suffered no apparent ill effects from complete obstruction to the duct. Also it seemed as if collaterals were rapidly developed subsequent to obstruction; but no proof of this was given.

A new departure in ligation of the thoracic duct was effected in 1898 by Stüler.[16] This author, after referring in uncomplimentary terms to the hypothesis of v. Schwerdt [17] regarding the pathology of Morbus basedowii with respect to the formation of subcutaneous collateral lymphatics, gave the results of his experimental work on the ligation of the duct in rabbits. Under aseptic precautions and ether anesthesia he ligated the thoracic duct high in the abdominal cavity, just below the diaphragm. Four experiments in all were made. In the first case the aorta was damaged and the animal bled to death; in the second case the diaphragm was ruptured at operation and the animal later died of peritonitis. The fourth animal also died of peritonitis. The third animal, however, survived and gained weight. A piece of the supposed thoracic duct removed at the time of operation showed microscopically that it actually belonged to the thoracic duct. The author intended to report later the findings in this animal, but no subsequent record is available.

Lucibelli [18] published the results of his work on the effects of ligation of the thoracic duct. He used two large dogs as his subjects and gave them milk four or five hours before the operation as an aid in identifying the duct. With chloroform or Richet's solution as anesthetics and with sterile precautions, the operation was performed in the left side of the neck. In the first dog the operative wound became infected and continued to discharge pus for from 20 to 25 days after operation. At the end of this time the dog ceased losing weight and began to gain; his general condition also improved. At the end of two months from the time of operation the animal was in fair condition and the various examinations of the different body fluids were made. These examinations were very elaborate and included a complete urine analysis, isotonicity of the blood, red, white and differential blood counts. As a control for these findings an entirely different dog of the same weight, but living under the same conditions, was used. The first dog gradually became worse and died 3 months and 11 days after the operation. Autopsy showed a spleen five times normal size, mesenteric glands hypertrophied, glands of neck large, large heart, liver and pancreas. However, no injections were made to see whether the ligation in the neck was complete. The second dog did not have any post-operative infection. At the end of three months the same extensive examinations of the urine and blood were made, and immediately thereafter the dog was killed. Autopsy showed no loss of weight as in the previous case; slight engorgement of lymph glands; spleen four times normal size; small amount of fluid in pleural cavities; nothing unusual otherwise was observed. There also followed an exhaustive description of the histological findings of the tissues removed from the two animals. From these data, Lucibelli concluded that complete ligation of the thoracic duct caused death in the dog; that partial ligation caused little disturbance because collateral lymphatics established themselves soon; that complete ligation caused changes in all the organs and impaired their secretory function; that changes in the histological picture were due to the toxicity of stagnant lymph; and that of various causes for œdema, change in the lymphatics was one.

The most recent work on the lymphatic system that involved ligation of the thoracic duct, is that by Bunting and Huston.[19] These authors, in considering the fate of the lymphocyte, resorted to ligation of the left thoracic duct and jugular vein just before the duct entered, and in some experiments the neck lymphatic trunks on the right side were also tied. All their work was done on the rabbit. They found that this procedure, coupled with splenectomy, produced a marked but temporary decrease in the absolute number of lymphocytes in the circulating blood. They also noted the numerous anomalies of the thoracic duct, and in one case observed anastomosing lymphatic vessels leading through the thymus to the right side.

In the foregoing brief review of the literature regarding the ligation of the thoracic duct as it affects the general economy of the animal, it can be seen that a gradual change in the opinion concerning the importance of the thoracic duct has taken place. At first it was held that ligation of the duct was fatal because the necessary alimentary juices no longer

reached the blood stream (Cooper[9]). Then it was argued that only those cases in which the ligation was complete were fatal; whereas, when all the branches of the thoracic duct were not included in the ligation and chyle could thus get into the blood stream, the animal survived (Magendie[12]). Finally, it was believed, even complete ligation of the duct had no evil effect on the animal (Leuret and Lassaigne,[13] Schmidt-Mühlheim[14]).

Discussion of Literature

In considering the literature quoted above, it is evident that no conclusive work has been done on the question regarding the effects on the animal of complete ligation of the thoracic duct and its branches, as well as noting the effects of such a ligation after a comparatively long period of time. Duverney[8] obviously accomplished nothing with the ligations of the subclavian vein either proximal or distal to the entrance of the thoracic duct. Flandrin[3] anticipated Leuret and Lassaigne[13] by 30 years; yet he gave no evidence to support the complete ligation of the duct. Sir Astley Cooper[9] and Mayer[10] claimed that ligation of the thoracic duct is lethal. Cooper claimed that rupture of the cisterna chyli accounted for the extreme extravasations; however, Schmidt-Mühlheim[14] showed by injections that with similar extravasations the cisterna was not ruptured. Indeed Cooper did not describe the rupture to any extent, but considered it a matter of fact. Magendie[12] believed that death of the animal at the end of 5 or 6 days was due to the effects of the ligation and nothing else. In all probability these deaths were due to infection. Again, Magendie used injections to trace out the lymphatic paths, and in this respect his work was better than that of many investigators who worked a hundred years later. Leuret and Lassaigne[13] on the basis of one experiment found that ligation had no evil consequences. However, they operated only on one side of the neck, satisfied themselves by dissection without the aid of previous injection that the duct really was tied off; postulated that the chyle took a different course, namely, from the cisterna chyli to the portal vein, and proved this again to their own satisfaction, by simply ligating the portal vein and finding, as a result, some blood in the cisterna chyli. Colin[4] after numerous experiments on various domestic animals came to the same conclusion as Magendie[12] 50 years before. In his first animal he obviously did not get all the branches of the duct in the neck successfully ligated. In the case of the two dogs that lived respectively 20 and 25 days after operation, infection was also probably the cause of death, since the animals refused all food and behaved so differently from other dogs in which the duct was really tied without infection. In this respect the careful work of Schmidt-Mühlheim[14] is noteworthy. Up to this time all operative work had been done without antiseptic or aseptic precautions, and although "perfect suppuration" took place, nevertheless, this very fact vitiated practically the entire experiment. Schmidt-Mühlheim made the first serious attempt to prevent the chyle from reaching the blood stream; and furthermore, he used injections to make sure that the ligations were complete. It would have been interesting to know what would have taken place if the animals had been kept longer than seven days. Unfortunately, all the animals were sacrificed within a week from the time of operation. However, to tie off practically the entire superior vena cava is a considerable operation and a great shock to the animal; nevertheless, the animals recovered from the operation very satisfactorily. Even this operation would not necessarily always shut off the chyle from the blood stream, since it is possible that branches of the thoracic duct could enter the axillary vein distally to the point of ligation and eventually reach the heart through the collateral venous circulation which obviously would be established. The advantages of this operative procedure were at once recognized and frequently used by biochemists (Munk and Friedenthal[20]). Boegehold[15] also stated that ligation of the thoracic duct exerted no deleterious effect on the animal, basing his argument on clinical cases as well as on the result of his last experiment, in which he ligated the thoracic ducts according to the method of Schmidt-Mühlheim. In this animal he made a small injury to the duct, and three days after this found a small clot at the site of injury. Here the same objections can be raised as were advanced with Schmidt-Mühlheim; besides this, injection of the lymphatics was not made to ascertain whether the ligation was complete. The experiments of Stüler[16] are as novel as they are inconclusive. All that can be gathered from his work is that a complete ligation of the thoracic duct was attempted in the abdomen; that a large lymphatic trunk, probably the thoracic duct, was ligated; that the animal recovered and gained weight; and that the subsequent findings in the animal were promised but are not available. Lucibelli[18] tried to determine what effects ligation of the duct would have on the animal economy, particularly when studied several months after the operation. His animals were killed at the end of three months, which is the longest time any animals with ligated thoracic ducts were ever allowed to survive. Unfortunately, his work is not without serious objections. In the first place he ligated the duct on one side of the neck only, although previous work, particularly that of Schmidt-Mühlheim,[14] had shown how frequent it was that branches of the thoracic duct went to the right side, and how essential it was to ligate not only the thoracic duct on one side, but also to ligate the large veins in the base of the neck on both sides, as well as to ligate the right thoracic duct. That the dog is no exception in having many anomalies in the entrance of the thoracic duct into the veins was previously emphasized by Kulferath.[21] In the second place, one of the two animals had a postoperative infection lasting nearly a month. This infection alone discounted the value of the results obtained by careful chemical analysis of the urine and blood. Again, he used as controls, not the same animal before operation, but preferred an entirely different dog of about the same weight as the experimental animal and kept under the same conditions. Also, judging from the urinary findings, the first animal had what Lucibelli called a chronic interstitial nephritis. Accordingly, no animal with a kidney lesion, even though the thoracic duct be securely tied, could be compared

with a normal animal, particularly in so far as the urinary findings are concerned. The presence of the infection vitiated also all conclusions regarding the histological changes purported to be consequent to a thoracic duct ligation. There is, furthermore, no evidence supported by post-mortem procedures to substantiate the conviction that the ligations were successful; and the absence of confirmatory examination alone makes the whole work faulty. It is needless to discuss the author's contention that his two experiments support the view that œdema is due to stagnant lymph formation. Finally, in the work of Bunting and Huston [19] there was no evidence to support the belief that the thoracic duct was completely ligated. Their work did show that the rabbit is also no exception to the general rule which holds that the entrance of the thoracic duct into the veins of the neck may be extremely varied.

Before proceeding to the experimental work, it may be added that numerous investigators (Kunkel,[22] Fleischl,[23] Kufferath,[24] Harley,[25] Josué,[26] Wertheimer and Lepage,[26] Davis and Carlson [27]) also ligated the thoracic duct and studied the effect of simultaneous ligation of the biliary duct, or subsequent changes in the number of lymphocytes in the blood. None of these authors operated in a way to preclude all possibility of anomalous collateral circulation, nor did all inject their specimens post-mortem to be sure of the course of the lymph.

The Russian literature also contains reports of work done on the ligation of the thoracic duct. Some of the work is experimental (Khlopin [28]), in which the absorption of fats was studied; others (Vitlin [29]), reported a case of injury to the duct, and reviewed the literature on other cases of injury to the duct. It is interesting to note that Vitlin [29] and Temkin [30] took the same case from the clinic of Professor Rotter in Berlin as a stimulus for their respective articles.

At the suggestion of Dr. Cunningham, and with his frequent advice, experiments were undertaken to determine what effect on the general economy of the animal ligation of the thoracic duct would have; also what collateral circulation, if any, would be established. It is a pleasure to thank Dr. Sabin and Dr. Cunningham for their interest and help during this investigation.

EXPERIMENTAL RESULTS

In all the experimental work the cat was used exclusively, chiefly because it is a convenient and very satisfactory laboratory animal, and also because the lymphatics of the cat have been described to a considerable extent. The animals were for the most part young adult male cats, seemingly in good health. Food was withheld for 24 hours before the operation which was performed under ether anesthesia and with strict aseptic precautions. During the operation, the animal received the benefit of hot-water bottles and after operation it was placed in a warm cage. All the animals were weighed immediately before the operation and at various times after the operation.

Operative Procedures.—At first, attempts were made to ligate the thoracic duct in the neck. In these cases the animals were fed cream five hours before operation in order to make the duct more conspicuous; at times this advantage was heightened by adding Scharlach R to the cream. Several of these operations were successful in so far as injections from below showed that the duct had been effectively ligated. But it was soon evident that this procedure did not produce enough positive results to make it reliable for work which required absolute ligation of the duct, for frequently the duct had numerous entrances into the veins of the neck, and it was not possible to operate without feeling doubtful about the ligation of all the branches.

Accordingly it was decided to try to ligate the duct high up in the chest, before all the anomalous branches were given off. Because of the consequent pneumothorax following opening of the chest, intratracheal ether was given. A calibrated No. 13 F soft rubber catheter with accessory openings at its end was inserted into the trachea. Air for the apparatus was supplied by a foot bellows which was connected to a mercury safety valve adjusted to 20 mm. of mercury, and led over ether in a Woulfe bottle, which was further provided with a by-pass direct to the catheter. With this apparatus all gradations from pure air to heavily saturated ether vapor could be administered at physiological pressures. The operation consisted in going into the second or third intercostal space, spreading the ribs apart, isolating the carotid artery and vagus nerve, inclosing as much of the surrounding tissue as possible in a ligature, and closing the cavity. This operation also was not successful, because isolation of the vagus nerve and carotid artery was often difficult, and besides branches of the duct to the right side were completely missed by this undertaking.

The Operation.—Finally it was decided to operate lower down in the chest, and this procedure gave the desired results. The animal was placed on its right side, with the left front leg drawn a little upward and forward. The left side of the chest was shaved over an area extending from the third to the tenth intercostal spaces, and from the midline in the back to the parasternal line. Iodine technique to the skin was employed. A transverse incision about 4.5 cm. long was made over the sixth or seventh intercostal space, extending forward from a point about 4 cm. from the midline of the back. Dissection was carried down to the latissimus dorsi muscle, the fibers of which were split longitudinally. By palpation the desired intercostal space was determined and dissection was carried down through the serratus muscle to the superior border of the rib bounding the inferior portion of the intercostal space; this was done to avoid damaging the intercostal vessels which course superiorly. One was sure of good exposure when it was necessary to cut a few lateral fibers of the sacrospinal muscle. The intercostal muscles were then severed along the superior border of the rib, care being taken to cut to a uniform depth. After the pleura was reached, the tip of a pair of blunt-pointed scissors was thrust into the pleural cavity and the opening enlarged. A small pair of self-retaining rib retractors were inserted and the opening widened to about 3 cm. The lungs collapsed considerably and did not interfere with further work, particularly when the intratracheal pressure was kept low.

The thoracic duct was usually not seen because it contained no chyle. The adventitia over the anterior surface of the aorta was grasped with forceps and drawn slightly toward the opening. The adventitia inferior to the forceps was then carefully dissected from about the aorta as much as possible and an aneurysm needle with a fine silk thread was passed around the aorta; this thread served as a traction suture on the aorta. A right-angled aneurysm needle was then inserted from the left to the right side of the aorta and under it, and turned through an angle of 180°, so that the point rested on the right side of the vertebral column near the midline. The point was allowed to pass along the vertebral column to the left side until it appeared at the sympathetic chain. The tissues included in this ligature were the thoracic duct and sometimes the azygos vein. The aneurysm needle was then passed under the aorta from its right to its left side, the tissues of the previous ligature were again included, but chiefly was it desired to get the tissue between the vertebral column and the esophagus. Sometimes it was necessary to include more tissue about the esophagus in a third ligature; the ligation was thus completed. The ribs were approximated with a double medium silk suture; interrupted sutures for the muscle; the usual subcuticular stitch for closure. No dressing was applied but the iodinized area was carefully washed with ether to avoid any iodine irritation with consequent damage to the incisions. The entire operation from incision to closure did not take more than half an hour.

Post-Operative.—The animals made a satisfactory recovery following operation. They frequently ate on the day after operation. There was no evidence of diarrhœa, œdema or respiratory distress; slight abdominal tenderness was frequently observed. The animals were weighed at intervals following the ligation; the results were not uniform. Some of the animals gained weight, some lost, whereas the one which was sacrificed 66 days following the operation, and showed absolute ligation of the duct, evidenced little change in weight. On a series of animals leucocyte counts and differential blood counts were made to study chiefly the lymphocyte change following the operation. This work will be reported later.

The cats were sacrificed from 24 hours to 77 days after ligation. Under ether anesthesia the abdomen was opened and the mesenteric lymphatics of the small intestine were injected with a saturated aqueous solution of Berlin blue. The ordinary hypodermic syringe with a No. 28 needle was found to be preferable to larger Record syringes, since the pressure of injection could be regulated better. The chief point in injecting the mesenteric lymphatics was to avoid any possible injection of veins, for if the dye reached the blood stream other than through lymphatico-venous communications, the experiment would be inconclusive. Thus, if the subserous layer or muscular coats of the intestines were injected, then the dye could possibly enter the veins as well as the lymphatics. The same objection held for the mesenteric lymph gland, since a direct injection of a lymph gland would also entail the possibility of striking veins as well as lymphatics. During the injection of the last cubic centimeters of the dye, the animal was killed, and the injection was continued until the ventricle stopped beating. This was done to insure a sufficient amount of dye at the lymphatico-venous communications. The blue pigment was usually seen in the lungs after the chest was opened and the course of the injection with respect to the thoracic duct studied. Frequently the animal died during the course of the injection from a pulmonary embolus caused by the injected material. Material for sections was cut from various organs; the remainder of the animal, except the head and extremities, was fixed in formalin and saved for further dissection.

Types of Collateral Circulation Found after Ligation of Duct

As a result of these dissections, two general types of collateral circulation were established. The one type consisted of a collateral circulation to the right thoracic duct, the other type comprised those cases in which the lymph entered the azygos vein or its branches.

The first type is illustrated by Fig. 1 which shows the collateral circulation established to the right thoracic duct. It may thus be justly said that this case illustrates absolute ligation of the thoracic duct and the periaortic lymphatic plexus. The animal from which the figure was drawn was sacrificed one week after operation. The structures of interest were taken out *en bloc*, dehydrated and cleared in oil of wintergreen. Attention is called to the absolute ligation of all lymph drainage to the left side of the neck. Below the point of ligation is a small but significant lymphatic plexus supplied by a large branch coming off from the thoracic duct. From the superior aspect of this plexus a small branch is seen to course on the azygos vein to a small gland at the mouth of the subclavian vein, and from there two trunks finally join and empty into the junction of the jugulo-cephalic trunk and the internal jugular vein.

Attention is also called to the general appearance of the abdominal lymphatic vessels soon after ligation of the thoracic duct. An œdema developed about the large lymphatic vessels, particularly around the cisterna chyli and its large trunks. This œdema depended in its appearance on the nature of the fluid in the lymphatics. If these were laden with chyle, the œdema was chylous in nature; if no chyle were present, the perivascular tissues were bathed in a limpid, slightly yellow-tinged, clear fluid which seemed to contain small fatty droplets. In no case did this œdema resemble ascites to any degree. Likewise, the cisterna chyli was never found ruptured. This œdema in some animals became well established at the end of 24 hours, and persisted for one week, as was shown in a case in which a marked constriction, but not occlusion, of the thoracic duct was secured.

The lymph glands underwent marked hypertrophy. They had a fatty appearance, and showed the small follicles on the surface. They were very œdematous, and on section a considerable amount of clear, colorless fluid escaped. The increase in the size of lymph glands was more impressive in regious where they were ordinarily small and scarce, *e. g.*, between

the large mesenteric gland and the small intestine. Occasionally, glands of the size of almonds were seen in this region. In no case did the spleen seem larger than normal. The thoracic duct above the point of ligation was usually small and contracted.

In none of the dissections was the vagus nerve included in the ligature; occasionally, the left sympathetic chain was taken. Nor did the pigment reach the lungs via the direct lymphatic communication between the lungs and the cisterna chyli (Cunningham[21]).

The second type of collateral circulation is shown in Fig. 2, which was drawn from a specimen in which the subject was sacrificed 66 days after ligation. The thoracic duct with the entire lymphatic plexus was ligated. The azygos vein was included in the ligature and thus precluded any collateral vessel developing, as illustrated in Fig. 1. It is seen that an extensive lymphatic plexus has developed at the cisterna chyli and the azygos vein. Specimens of the contents of the azygos vein removed near the lymphatico-venous junction as well as a little further along the course of the vein, and examined under the microscope, revealed the Berlin blue pigment.

In one animal that was sacrificed three weeks after complete ligation, the lymphatico-venous connection was in the ninth left intercostal vein just before the latter entered the azygos vein. The communicating vessel took a tortuous path, commencing at a point on the thoracic duct at the level of the entrance of the ninth intercostal vein into the azygos vein, turned inferiorly and extended 7 mm. along the left side of the aorta, giving off small branches which entered the walls of that vessel; made several small sharp turns and extended about 4 mm. superiorly and laterally; then went medially and slightly inferiorly, making an acute angle with the ninth intercostal vein which it entered about 6 mm. from its junction with the azygos vein. This communicating vessel was almost the size of the intercostal vein, and was undoubtedly taking over the function of the thoracic duct.

In another case, a lymphatico-venous communication probably existed between a branch of one of the left lumbar veins and the cisterna chyli, since the blue pigment was found in the distal part of the lumbar vein, but in much greater quantity at the entrance of the lumbar vein into the inferior vena cava. As the connection was not actually seen, the absoluteness of the junction cannot be claimed.

Retrograde Injection of Lymphatics

Before entering into the discussion of the above findings, attention is called to the retrograde injection of lymphatics as found in the majority of the dissections. In studying the lymphatic distribution in embryos by the injection method, advantage is constantly taken of the fact that specimens up to 5 cm. in length have the valves in their lymphatic vessels incompletely developed or entirely absent, and accordingly allow extensive retrograde injection of their lymphatic vessels (Sabin,[22, 23] Heuer,[24] Cunningham[21]). In observing the relation of lymphatic vessels to connective tissue in pig fœtuses by means of injections, MacCallum[25] noticed that the valves were not very competent. In the adult, retrograde injections of lymph vessels entering the cisterna chyli and regional visceral lymph glands have been described by Schmidt-Mühlheim[11] and Bartels.[26] While injecting the mesenteric lymphatics, as above described, frequently one could see contributing branches of the vessel which was being injected centripetally gradually suffer retrograde injection through the successive dilatation of the intervalvular segments and the incompetence of their respective valves. In several cases such retrograde injections were carried to the subserous coat of the small intestine; while other cases showed a retrograde injection through the lymph glands draining the kidney with the afferent lymphatics injected as far as the hilum of that organ. Likewise, injections of small lymphatic vessels in the adventitia of the aorta and of vessels on the surface of the psoas muscle have been seen. Again, the large lymphatic plexus draining the liver and gall-bladder has been observed in a markedly dilated though uninjected state. In no case, however, have the parenchymatous lymphatic vessels been filled; and this in spite of the fact that these vessels are supposed to have either no or only a few valves (Bartels,[26] p. 71). The problem seems to lie in emptying lymphatic capillaries before injections are made; this condition may possibly be achieved by introducing hypertonic solutions into the blood stream, thus emptying the lymphatic capillaries and allowing the injection mass to enter. Waldeyer,[27] in 1867, called the attention of pathologists to the possibility of retrograde lymphatic transport of metastases.

Discussion

A new method has thus been described for ligating the thoracic duct. While ligations of the duct have been performed in the neck and in the abdominal cavity by other workers, no attempts, it seems, have been made to secure ligation in the chest, although the duct has been wounded frequently in that cavity for experimental purposes (Boegehold[18]). The operation can be performed without extensive dissection and without ligation of large veins (Schmidt-Mühlheim[11]); it can be performed speedily and with a considerable guarantee of success. The method has provided experimental animals with absolute ligation that have lived apparently unaffected as long as 66 days after the operation. This period of survival of the animal in this study may be compared to the report of Lucibelli,[19] in which it was stated that the longest period of survival after ligation of the duct was three months and eleven days, but in this work of Lucibelli there is much reason to believe that the ligation was not absolute. However, from the above experimental results, one can conclude that the integrity of the thoracic duct is not essential to the life of the animal.

Furthermore, the method of injecting the mesenteric lymphatics avoids all possibility of injecting the venous system inadvertently, and has provided excellent examples of retrograde injections of the lymphatic vessels. Naturally, previous ligation of the thoracic duct may have played a considerable rôle in facilitating these injections.

It is interesting to note to what extent the present knowledge of the embryology of the lymphatic system may be util-

ized to explain the experimental findings. However, although it is not the purpose of this article to enter into the discussion of the various views regarding the origin of the lymphatic system (Huntington,[28] Sabin,[29] McClure,[30] Lewis,[31] Pensa[32]), it can be stated that at one time in embryonic life a large lymphatic plexus exists extending from the veins at the base of the neck on either side, down around the aorta, and terminating in the cisterna chyli; also, that the lower part of the embryonic thoracic duct is bilaterally symmetrical. The branch leading from this plexus to the right thoracic duct may also be considered a part of the embryonic plexus; the fact that it enters a gland first before proceeding to the veins suggests that it was originally one of the smaller and more remote portions of the plexus. In another animal which was sacrificed 77 days after ligation, this small connecting vessel had a counterpart in two huge trunks, each of which was almost the size of a normal thoracic duct; the corresponding gland was also markedly enlarged. This response of embryological

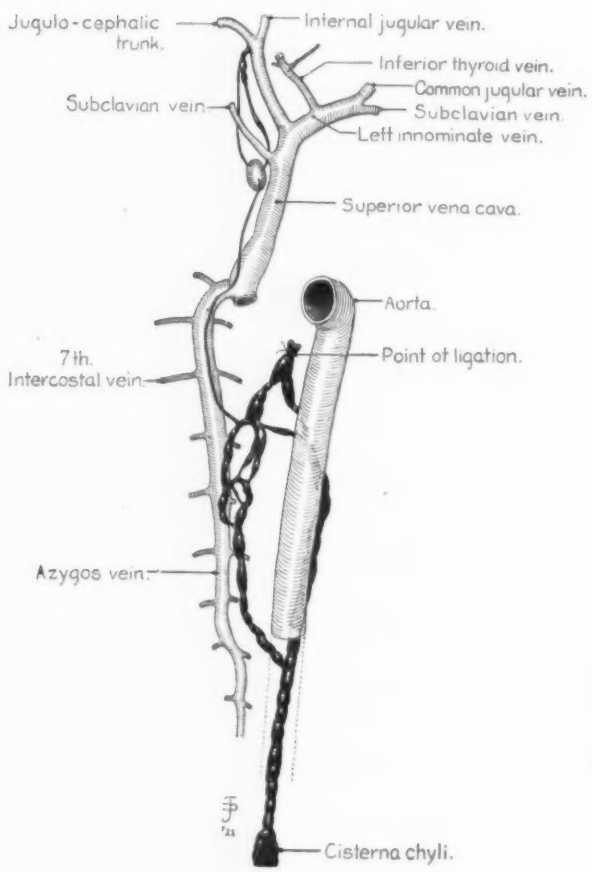

Fig. 1.

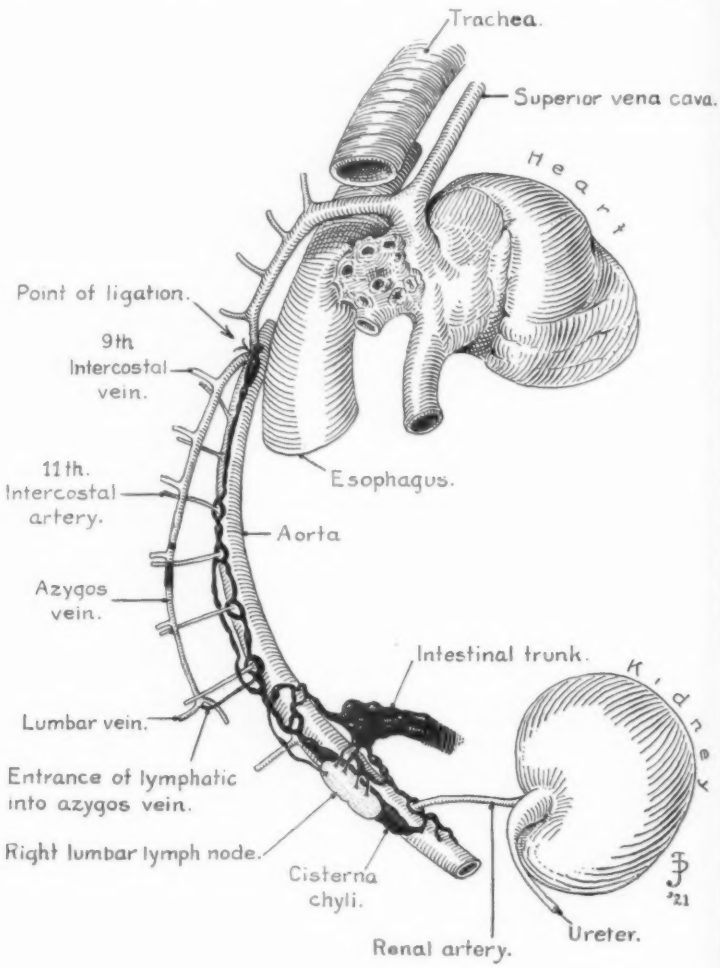

Fig. 2.

origin of the thoracic duct in the pig has been described by Baetjer.[33] With these embryological data as a basis, Davis[34] described and explained various types of thoracic duct anomalies, and it is interesting to note to what extent Fig. 1 fits in with some of the schematic representations of embryonic lymph channels that he depicted. Thus the small plexus developed below the point of ligation may well represent a portion of the embryological lymphatic plexus which normally does not function, but which, in response to the ligation, may have been forced to enlarge and dilate. Again, the small non-functioning lymphatic capillaries in a physiological capacity, if true, recalls in a measure the important work of Krogh[35] in relation to blood capillaries.

On the other hand, it is impossible to explain with our present knowledge of embryology, the connection between the thoracic duct and azygos vein, as illustrated in Fig. 2. It seems as if the earliest stages in the development of lymphatic vessels are as yet unknown. The recent work of Sabin[29] on the development of blood vessels would suggest that the differentiation of angioblasts as well as the sprouting of the vascular

endothelium could lead to the formation of lymphatics at other places along the venous system than from the anterior cardinal veins or from the veins of the Wolffian body. Thus, they could arise from the azygos vein, form a plexus with those lymphatic vessels arising from veins at the usual places, and gradually become small and functionless until physiological exigencies, produced, for example, by ligation of the thoracic duct, caused them to enlarge and function. Again, that large venous network in the early embryo which is associated with the azygos vein and which later disappears may be a factor in producing this lymphatico-venous connection.

E. R. Clark,[47] in the description of a very curious anomaly of the thoracic duct, considered the embryology of the lymphatic system in the explanation of the condition. Likewise, clinical cases of lymphatico-venous fistulæ have been discussed on this basis (Halsted [48]).

Again, the establishment of collateral lymphatic circulation may occur through the regeneration of lymphatics. However, the studies in the regeneration of lymphatics have not been extensive enough, nor do they carry the necessary conviction (Meyer [49]). As much as one is inclined to believe in the regeneration of lymphatics—and this could easily explain the result as illustrated in Fig. 1—nevertheless, the necessary experimental proof seems lacking.

Since several cases of lymphatico-venous communications have been found (see Fig. 2), the subject of these connections is brought up for consideration. A host of writers (see Bartels [50]), as early as 1662, had described unusual lymphatico-venous connections; and numerous other investigators have attempted to disprove the evidence. Boddaert,[50] in 1899, described in the rabbit a connection of the thoracic duct with the azygos vein. Leaf [51] in 1900 maintained that the azygos vein received many lymphatic vessels. However, Bartels,[50] in 1909, questioned the correctness of any such lymphatico-venous communications. More recent work had thrown new light on the subject. Silvester [52] described the presence of permanent communications between the lymphatic and the venous systems at the level of the renal veins in adult South American monkeys; Baum [53] described cases where vasa efferentia of lymph glands emptied directly into veins; Job [54,55] reported lymphatic communications with the inferior vena cava, ileo-lumbar, renal and portal veins in rats. It seems, then, well established that the lymph does not necessarily have to enter the venous system at the base of the neck.

The presence, then, of these lymphatico-venous connections enters into the problem of fat absorption. The entire anatomy of the chyliferous portion of the lymphatic system suggests that the newly absorbed fat avoids direct entrance into the liver. Biochemists, even with refined methods for determining fats in body fluids (Bloor [56]), can recover from the thoracic duct only 60-70 per cent of the previously ingested food fats, but they are at a loss to explain the disposal of the remaining 30-40 per cent. Munk and Friedenthal [20] found that the blood fat increased after the thoracic duct had been tied. D'Errico [57] maintained that the percentage of fat in the portal vein was normally greater than that in the jugular vein, also that, following ligation of the thoracic duct, the fat content of the portal vein with respect to the solid residue decreased but still remained higher than that of the jugular vein. He also believed that ligation of the duct accentuated lymphatico-venous communications. It is obvious that lymphatico-venous connections have been a generally unrecognized factor in all these studies of fat absorption involving ligation of the thoracic duct; and consequently these investigations are open to criticism.

Albrecht v. Haller, Albin and Hebenstreit are reported by Boegehold [15] to have seen the thoracic empty into the azygos vein. Wutzer,[58] while demonstrating the course of the thoracic duct in the body of a woman 37 years old, noticed that there were three connections between the duct and the azygos vein; also, that above these connections, the duct became attenuated and fibrotic. This case seems to show that in regard to this lymphatico-venous connection there is an analogous relationship between the human subject and the laboratory animal.

However, in spite of this analogy, one cannot claim with absolute surety that ligation of the thoracic duct in the human subject would prove equally inocuous. Yet it is clear, from the current surgical text-books as well as from the individual reports of injury to the thoracic duct, that there is no accepted method of treatment. Usually one of the four procedures is employed when the duct is injured: (1) Repair of the wounded duct and provision for subsequent ligation if necessary; (Cushing [59]); (2) tamponade; (3) ligation of the vessel or (4) implantation of the severed duct into a vein (Harrison [60]). Convalescence is the rule. Cushing considered that in case of ligation of the thoracic duct the lymph current would be reversed, and finally all the lymph would be taken up by the right thoracic duct—a postulate supported in a measure by these experiments. A record of numerous clinical cases involving injury to the thoracic duct with a discussion of their treatment has been given by Zesas.[61, 62] However, it is very questionable whether all the injuries to the thoracic duct really constituted injuries to the main trunk. Large lymphatic vessels from the head and neck often join the duct before its entrance into the vein and may be mistaken for the duct itself. Again, the presence of chyle does not guarantee the vessel to be the main trunk, because there frequently are several branches of the duct before its entrance into the veins.

In short, then, with the aid of the above experimental data, treatment of thoracic duct injuries would resolve itself into: 1, Repair of the injury if possible; or, 2, ligation. There is every reason to believe that similar treatment would apply to injury of other large and important lymph vessels; *e. g.*, the intestinal trunk.

SUMMARY

After reviewing the literature on the experimental ligation of the thoracic duct, an intra-thoracic method has been described for complete ligation of the thoracic duct in the cat. It seems that the integrity of the thoracic duct is not essential to the life of the animal. In some cases in which the ligation was absolute, collateral lymph circulation was established to the right thoracic duct; while in other cases which showed

complete ligation, lymphatico-venous connections were found to exist between the thoracic duct and the azygos vein. The embryology of the lymphatic system may explain partly, but not entirely, these findings which also have a bearing on studies of fat absorption as well as on the clinical aspect of injuries to the thoracic duct.

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STUDIES ON EXPERIMENTAL RICKETS

XV. THE EFFECT OF STARVATION ON THE HEALING OF RICKETS

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We have shown elsewhere[1] that certain types of faulty diets induce bone changes identical with those seen in rickets in human beings. Cod-liver oil exerts a pronounced effect in preventing the development of these changes, or, once they are established, tends to cause the bones to return toward a normal condition.

The most effective way which we have found to demonstrate the therapeutic value of cod-liver oil is through the application of our "line test," which has been fully described in another paper.[2] Young rats are restricted to our diet (Lot 3143) which has the following composition for a period of 35-40 days.

Lot 3143

Wheat	33.0
Maize	33.0
Gelatin	15.0
Wheat gluten	15.0
NaCl	1.0
$CaCO_3$	3.0

Any other diet having identical dietary properties would serve the same purpose.

This diet contains proteins of good quality and in great abundance (about 33 per cent), and about twice the calcium necessary for optimal growth and nutrition. It is, however, low in fat-soluble A and below the optimum in its content of phosphorus. One hundred grams contains 0.3019 grams of phosphorus.

If young rats are fed on this diet they develop a condition of the skeleton which is identical with the most severe rickets seen in the child. In the bones of these animals (Fig. 1) the cartilage is overgrown and abnormally persistent. The shaftward margin of the cartilage is irregular and the cartilage is invaded by blood vessels from the shaft of the bone. Lime salts are not deposited in the cartilage, so that no zone of provisional calcification is formed. A wide zone of tissue is formed between the cartilage and the shaft proper of the bone. This is made up of blood vessels, connective tissue and marrow elements, and of cartilage cells in all stages of degeneration, reversion, and of metaplasia into osteoid tissue. This is the rachitic metaphysis. The cortex of the shaft of the bone and the trabeculæ of the spongiosa are surrounded by wide zones of osteoid tissue (uncalcified bone). No signs of abnormal resorption of bone tissue are to be found. These bones are very soft and at autopsy the animals show deformities of the skeleton which we have discussed in detail in a preceding communication.[1]

When a young rat has been restricted for 35-40 days to this diet, experience has shown that the cartilage and adjacent portion of the metaphysis in the long bones will be entirely free from calcium salts. If now cod-liver oil is administered to the amount of 2 per cent of the diet, calcium salts are deposited in the cartilage on the epiphyseal side of the metaphysis. This amounts to the reappearance of the provisional zone of calcification. From the work of Schmorl and others we know this phenomenon to be the beginning of the healing of the lesion. The deposited salts appear in longitudinal sections

of the bone as a fine line crossing the proliferative zone of the epiphyseal cartilage transversely.

We have found that the administration of cod-liver oil to the amount of 2 per cent of the diet causes the line of calcification to appear in the cartilage within five days.

We have recently observed that when young rats with rickets are made to fast for periods of three to five days (distilled water only being offered), healing begins in exactly the same way as it does when suitable amounts of cod-liver oil are administered.

Ten animals, as indicated in Table I, were fed on our diet No. 3143. At the expiration of the preparatory period they were placed in special cages and starved for 3-5 days.* They were then killed with chloroform and autopsied. The long bones were bisected longitudinally, immersed in a 1 per cent solution of silver nitrate, and examined under the microscope after exposure to light for the presence of a newly deposited provisional zone of calcification. The results of this gross examination were checked by the study of celloidin or frozen sections.

TABLE I

DATA DESCRIPTIVE OF RATS EMPLOYED FOR SHOWING THE EFFECTS OF FASTING ON THE INITIATION OF THE HEALING PROCESS IN RICKETS

Number of rats	Age in days when put on diet	Days on diet	Age in days at death	Days starved	Sex	Weight at death
1182	60	70	130	5	♂	82
1221	45	64	109	5*	♂	87
1341	45	49	94	2*	♀	101
1345	55	49	104	3*	♀	85
1358	60	55	115	3*	♂	125
1364	65	30	95	3*	♂	80
1365	65	30	95	3*	♀	80
1366	65	30	95	3	♀	68
1368	60	35	95	3	♀	75
1369	60	35	95	3	♀	75

* Found dead on the morning of the day indicated.

The results of starvation were controlled by the examination of animals which had been raised in the same cages on diet No 3143 at the same time, but had not been starved.† Not one of the starved animals failed to show reformation of the provisional zone of calcification, and other evidences of the healing of the rachitic process. None of the controls had a vestige of calcium in the cartilage or metaphysis.

Since we have found that even on diet No. 3143 rats which were exposed daily to sunlight in the summer from the beginning of the experiment did not develop rickets,[3] three methods are now known of inducing the deposition of calcium salts in the cartilage of the bones of rachitic rats, viz., through starvation, exposure to light, and through the administration of cod-liver oil.

It is difficult to think of any single explanation for the common effect produced by cod-liver oil, sunlight and starvation on the skeleton of the rat rendered rachitic by means of a faulty diet. The possibility has been suggested that the effect of cod-liver oil may be attributable to physical force of one kind or another. This view we have discussed more fully in another place. But even if the effect of cod-liver oil should be the result of a physical force rather than a chemical reaction it does not follow that one could generalize regarding the other vitamins and accept the view that they necessarily act in an analogous manner. The analogy between the effects on the body of vitamin preparations and of the hormones is so striking that we are not justified in hastily abandoning the view that the vitamins are organic substances. Two at least of the hormones, thyroxin and adrenalin, are definite organic compounds.

Starvation causes healing of the rickets in a rat just as do cod-liver oil and sunlight, and the mechanism of the deposition of calcium salts in the proliferative cartilage may be the same. But cod-liver oil and sunlight improve the general condition of the animal. This is indicated by increased growth, longevity, muscular activity, storage of fat, and sexual potency. Starvation, on the other hand, causes the death of the rat in a few days. Its effects on the animal are favorable only in that they cause the healing of rickets. The mode of action of the three agents must be entirely different. It seems necessary to think that sunlight and cod-liver oil act by enabling the cells to carry on, even when their food supply is unfavorable. In other words, they aid the organism to adapt itself to an adverse environment. Starvation, on the other hand, must produce healing of the rickets at the expense of other body tissues. We cannot disprove at present the possibility that the cell functions more effectively when it is relieved of the load which a faulty diet imposes on it. However, during starvation certain tissues are destroyed for the upkeep of the supply of nutriment for those whose integrity must be safe-guarded to preserve life.

We have shown that the administration of cod-liver oil is followed by healing of rickets in rats even when they are receiving a diet with a faulty calcium-phosphate ratio. It may be that during the disintegration of protoplasm, which is consequent upon starvation, some substance is liberated which permits the animal to readjust the salt ratio within itself. But although it is possible that starvation liberates from the tissues an organic factor or factors, such as are in cod-liver oil, it is not necessary to account for healing in this way. Providing calcium and phosphorus are present in the proper proportions, normal calcification of the skeleton will occur. When the defects in the diet are such as they happen to be in the diet which we employed in these experiments (diet No. 3143), it would only be necessary for phosphorus to be liberated into the blood stream from disintegrated protoplasm (muscle for ex-

* The cages employed for the fasting rats had wide mesh wire bottoms, so that the feces passed through, and it was impossible for the animals to eat their stools. No bedding of any kind was available for the rats to eat.

† We have sections from the bones of nearly 100 animals which were maintained on diet No. 3143 under the same conditions as our test animals. These served as an additional control for the test.

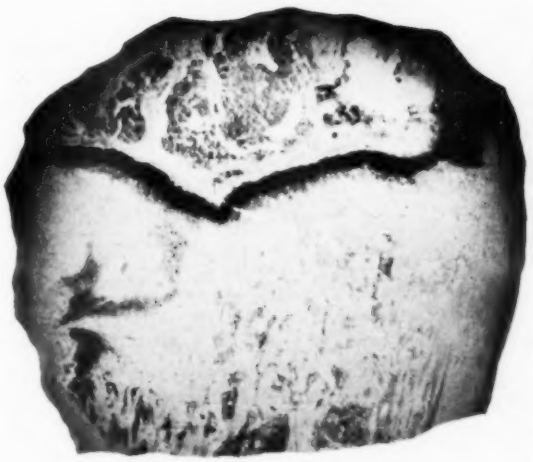

FIG. 1.—Photomicrograph of a section from the rachitic animal which had received diet No. 3143. There is no calcification of the epiphyseal cartilage or of the metaphysis.

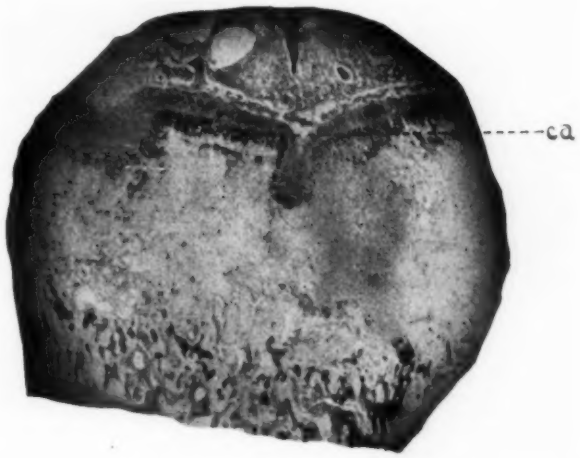

FIG. 2.—Photomicrograph showing the re-formation of a provisional zone of calcification (Ca) in the bone of a rachitic animal which had been starved for 5 days.

ample) in order to cause calcium deposition to occur in the cartilage. Animals on diet No. 3143, like rachitic children, have much less than the normal amount of phosphorus in the circulating blood. The administration of cod-liver oil or radiation from the mercury vapor quartz lamp causes the phosphorus in the blood to rise and it is not improbable that the healing of rickets which results from starvation is the immediate result of an equivalent increase of this element in the circulating blood. Just as soon as the load of a defective diet is removed and the body is forced to draw on its own tissues for maintenance of life and function, stored foodstuffs are released into the blood stream as the result of a process of selective tissue decomposition.

These experiments furnish the first anatomical proof of the beneficial effect of starvation on the animal body. The good effects of fasting are given a new meaning, because the organism is able to adapt itself to pathogenic distortions of normal metabolic ratios when the burden of carrying on exogenous metabolism is removed. Since the starving body is capable of readjusting abnormal relations within itself it is easy to understand the benefit derived by a diabetic from occasional hunger days, and why it is that the wasted athreptic infant does not develop rickets.

Rickets has certain of the characteristics of a deficiency disease because a certain substance contained in cod-liver oil and elsewhere corrects an anatomical condition which develops when the calcium and phosphorus in the diet are present in wrong proportions. Yet rickets has a feature entirely distinct from beri-beri, scurvy, and xerophthalmia. The relation between two inorganic elements determines the extent of the animals' need for the organic factor which cod-liver oil furnishes. No such relationship between a vitamin and any other food substance has been clearly demonstrated in any other condition.

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NOTES AND NEWS

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